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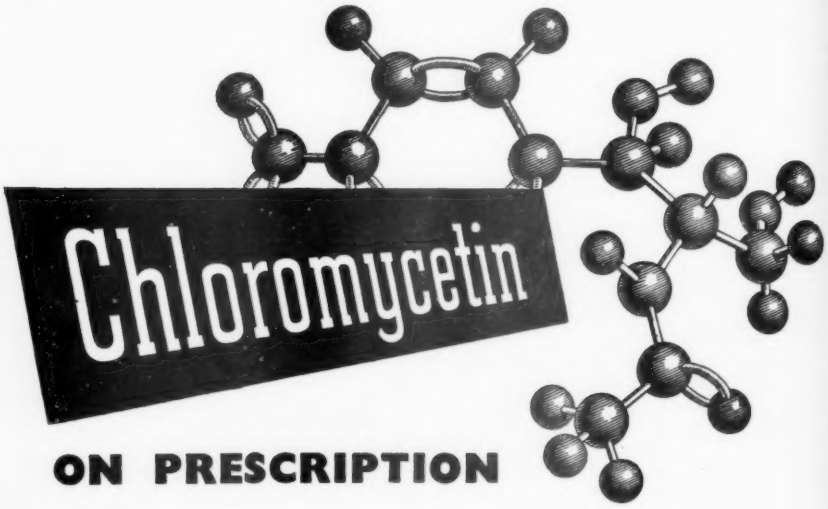

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Section of Experimental Medicine and Therapeutics

President—Professor R. A. McCance, M.A., M.D., F.R.C.P.Lond., F.R.S.

[*December* 12, 1950]

The Practice of Experimental Medicine

PRESIDENT'S ADDRESS

By Professor R. A. McCance, M.A., M.D., F.R.C.P.Lond., F.R.S.
Department of Experimental Medicine, Tennis Court Road, Cambridge

We have most of us a picture in our minds of what we mean by medical practice, both in its broader aspects, and in its narrower fields of general practice, consulting practice and so on. Each of these phrases conjures up something very real. To most of us the doctor comes to heal and we can picture his work: we appreciate the disciplines, responsibilities and the ethical background of the life of anyone who dedicates himself to such a service. Few people have such a clear picture of what the practice of experimental medicine involves; yet broadly speaking, those who set out to advance our knowledge of disease and treatment must sooner or later have recourse to experiment, for in the biological sciences experiment is the only sure way by which any advance can be established.

Claude Bernard's writings entitle him to be regarded as the father of experimental medicine but Harvey, Jenner and John Hunter were brilliant exponents of its possibilities long before his time, and the practice was already well established by the middle of the last century. Many of Claude Bernard's writings on the subject of experimental medicine do not require to be brought up to date. They are ageless. Changing customs and the passage of time, however, have created new situations and fresh problems and it is with these that I propose to deal.

Let us start with the word experiment, which most biologists use very loosely to cover any investigation, however trifling, made to advance knowledge. The term generally implies some deliberate change of conditions without foreknowledge of the results but with subsequent observation of them. It may be used, however, even when the conditions are not being deliberately changed, when the term observation would be more correct. Many doctors would not regard the attempt to cure an individual patient as an experiment, yet it undoubtedly may be, if the results are observed and followed up, for the essence of treatment is to do something positive to a patient, i.e. alter his conditions, in the hope that the effect will be of benefit to him.

People who are sick are often apprehensive. They long for reassurance which they do not find in the word "experiment". Worse still, the word may conjure up alarming possibilities in their minds. This is partly due to the activities of the antivivisection societies, partly to the casual use of terms such as "human guinea-pigs", partly to the atrocities which were perpetrated in concentration camps, and partly to the investigators themselves. The only comment made by a member of the governing body of the hospital when our department was being formed was that the name was an unfortunate one. I hope it was not, for I think it was the correct name, and we shall certainly do our best to prove it.

There is one fundamental difference between the investigator and the physician.

A good investigator may be as full of bedside charm and therapeutic ability as a good physician, but he must primarily be interested in his problem. The physician is interested first, last and all the time in his patients, and he has little sympathy with the attitude of the man who appears from time to time in the wards with a request to be allowed to disturb in some way one of his patients who may just be turning the corner after a critical illness. It goes against the grain to allow his patients to be used for a controlled therapeutic experiment if it means deliberately withholding from half of them the treatment which he believes, albeit unjustifiably, will do them good. He forgets, indeed he may not even know, that what he would have regarded as an "unjustifiable experiment" five years ago may have become one of his standard diagnostic or therapeutic procedures. The investigator finds it equally difficult to see eye to eye with a colleague who can alter a patient's treatment in the middle of one of his experiments without even letting him know, so nullifying two or three weeks of his work. Tact and a spirit of mutual co-operation and understanding are the only solutions. Taking a little trouble to develop new micro-methods often gives the entrée to a children's department, and placing a few beds at the disposal of an investigator often allows him to organize and complete good work to everyone's satisfaction and benefit.

Patients provide the problems, and disease may produce conditions which could never have been achieved experimentally and which demand detailed investigation, but if the illness is acute and treatable it is usually unjustifiable to withhold the remedy for long enough to make all the observations desirable in a satisfactory experiment. Chronic disease offers greater opportunity, but the basis of all successful experimentation is control of the conditions, and in the wards this may be very difficult. It is often much more satisfactory to work on normal men and women. Normal men and women are ideal for all physiological experiments when the "stress" originates in the environment, and some of the metabolic disease states can be reproduced in normal people. I have never had much difficulty in obtaining the co-operation of normal subjects. It is always a great help to have made the same experiment on oneself first and to be prepared if necessary to do so again. This is certainly true of metabolism experiments. Students make good subjects for some tests and they have frequently been employed, but in my experience they are not the best subjects for most experimental work. They can seldom give the necessary time for metabolism experiments, and they are often so overcome by the sight of blood that the complication of a faint is introduced into any test involving its removal. An experienced laboratory worker, male or female, is infinitely preferable. Subjects can, I believe, be hired for experimental work in some countries, and this may be a satisfactory arrangement, but I should be sorry to see this kind of service placed upon a commercial basis in this country. In the United States the patient is expected to contribute materially towards the expenses of his stay in hospital and he is generally anxious, therefore, to make this as short as possible. The hospital, in fact, may have to be reimbursed if a patient's discharge is delayed for experimental work, or if a special admission is made for such purposes. Valuable work was done by groups of conscientious objectors during and just after the war, and this is a form of national service which might very well be encouraged if the volunteers have the necessary mental and physical balance. Service personnel are now being employed for some experimental work on the physiological effects of heat and cold, high and low atmospheric and other gas pressures, and the stresses and strains of warfare. These men volunteer for the work and for some purposes they may be excellent.

Those who practise experimental medicine are naturally most interested in human disease and physiology and, as Claude Bernard put it: "Il est bien certain que pour les questions d'application immédiate à la pratique médicale, les expériences faites sur l'homme sont toujours les plus concluantes." Nevertheless, the advantages of

turning to animals are numerous, and the greater part of the work of a department of experimental medicine is often carried out on them. They can be obtained as and when required; their size is often convenient; they can be killed if necessary. Greater numbers of small animals than of human beings can be used and a better statistical result obtained. Their rapid rate of reproduction and short life span are invaluable for work on nutrition, genetics and carcinogenesis. In fact, once the investigator has posed his problem to himself he generally looks around for the most suitable animal on which to study it, and his choice often makes for success or failure. "Le choix intelligent d'un animal présentant une disposition anatomique heureuse est souvent la condition essentielle du succès d'une expérience et de la solution d'un problème physiologique très important." Claude Bernard was right but it is not always possible to reproduce in animals the set of conditions which have been under observation in man, and many since his time have forgotten that what has been proved for one species may not hold for another, and one of the attributes that makes for success in experimental medicine is the instinct which tells a man when to check his results on a second species, and above all when to turn from animals to man, or *vice versa*.

There is no difficulty about working with animals in this country, provided suitable accommodation can be found for them. One must comply with the Law relating to experiments on animals, but few people would wish to do otherwise. A licence is obtainable for any justifiable work on living animals. The investigator then has to make an annual return of his experiments and his animals are periodically inspected, but he benefits in that he is protected from unauthorized interference. The Authorities at the Home Office have always been most helpful to me. A licence is not required to kill animals, so that any of their tissues may be obtained immediately after death for chemical, metabolic or pathological work without let or hindrance.

There is no difficulty about making some kinds of experiments on one's fellow creatures, and they are the only mammals for which a vivisection licence is not required in this country, but the use of man as one's experimental material raises all kinds of issues, moral, ethical and legal which have never really been faced and which, in my opinion, should be faced. A hundred years ago the issue was clear. "On a le devoir et par conséquent le droit de pratiquer sur l'homme une expérience toutes les fois qu'elle peut lui sauver la vie, le guérir ou lui procurer un avantage personnel. La principe de moralité médicale . . . consiste donc à ne jamais pratiquer sur un homme une expérience qui ne pourrait que lui être nuisible à un degré quelconque, bien que le résultat pût intéresser beaucoup la science, c'est-à-dire la santé des autres."

We should, I think, for present purposes, regard anything done to a patient, which is not generally accepted as being for his direct therapeutic benefit or as contributing to the diagnosis of his disease, as constituting an experiment, and falling, therefore, within the scope of the term experimental medicine. The definition, however, should not include all those unplanned experiments which are inseparable from the admission of any child or adult to a hospital, and which are often attended with considerable physical and psychological dangers, nor should it include the administration of established prophylactic remedies, even though some of them, particularly the attenuated viruses, may involve risk. The experiment visualized may be one of omission and consist of withholding treatment from a "control", or it may be one of commission and consist of making some test on a patient for which there is no obvious and immediate need. Whatever the problem interesting the investigator, however, it is, of course, true to say that the results of such tests must always help to characterize the diseased state and when known may sometimes be of benefit to the patient on whom the tests have been made. There is a case to be made out for regarding all these tests as being "investigations" conducted in the sufferer's best interests and therefore not constituting an experiment made solely for the advancement of knowledge. Wassermann reactions are carried out on every patient admitted to some

hospitals and every patient entering the Mayo Clinic is, I believe, subjected to an elaborate series of investigations. The real distinction is a subtle one and may depend upon the mental approach of the man who makes the tests. Nevertheless, I regard collecting an extra specimen of urine or taking an extra 5 c.c. of blood from a vein puncture, made purely for established diagnostic or therapeutic purposes, as falling within the range of the term "experiment". I would certainly regard weighing a baby "unnecessarily" as an experiment. Some people may think I am taking up a ridiculous attitude over this, but if an experiment is not defined in this way, where is the line to be drawn?

All experiments involve some risk. It may be an infinitesimally small one, but it is always there—you, or the nurse, may drop the baby for instance. If the experiment involves special vein punctures, or perhaps infusions, the risk is considerably enhanced, but it still remains immeasurably small in the hands of an experienced operator. Nevertheless, I have myself seen and experienced the most alarming effects from pyrogens and I think it quite likely that the virus which gave me a mild attack of jaundice in 1939 reached me through a syringe. In assessing the risks involved in any experiment and therefore the justification for doing it, there are many factors which require consideration. The skill and experience of the investigator are important ones, but so is the place where the experiment is to be performed. A procedure which would be perfectly safe in a well-equipped and well-staffed establishment might be quite unjustifiable somewhere else. A well-trained person is much less likely to make a mistake over a drug or its dosage than an untrained technician in a badly staffed hospital. I have recently given this question a good deal of thought in connexion with our work in Germany and other "field" work.

The mention of assistants brings me to another point. Many experimental workers are not qualified in medicine, and yet they take part in hospital work and experiments on normal people. Could they conceivably be regarded as "unqualified assistants", and what would be the position if an accident were found to be due to one of them? If a foreign medical man has come to this country to work in a department of experimental medicine it has, since 1947, been possible for him under the Medical Practitioners and Pharmacists Act to have his name placed temporarily on the Medical Register. This legalizes his position and if he can then join one of the Medical Defence Unions he and the department should be fully covered.

If an experiment is the first of a series it involves much more risk than one which has been made many times before by the same people out of the same bottles. I never worry at all, however, about trying out an unknown substance on man, for with a little patience one can work up the dose on oneself or other normal people so gradually that the risk can be reduced to vanishing point, but I do not think I would ever have had the temerity to carry out the first hepatic biopsy or cardiac catheterization. Our pioneer studies of renal function in newborn infants were made on babies which had been born with inoperable meningo-myelocœles. Hundreds of these experiments have now been made on normal newborn and on premature infants in other countries—yet I am still hesitating about doing so.

The risk involved in any experiment depends very much on whether the investigator knows that he will always retain control of the situation. An experiment on salt deficiency or dehydration can be pushed till the subject is showing severe effects, because the remedy is available all the time. To inoculate someone with icterogenic serum is a risk that I personally would never take, nor would I ever have cared to take it even before the risks were so well known, for once the inoculation had been made, I would have lost control. Everyone working experimentally with normal human subjects or with patients must remember not only his responsibility to the subject or patient but also his responsibility to the discipline of experimental medicine. One irresponsible experimenter can do great harm to medical science.

No experiments can be carried out on a healthy colleague without his co-operation and consent and any elaborate experiment should be preceded by a medical examination; the same thing applies to a healthy child. It would also, I believe, be regarded as an offence under common law to make any investigation upon a child which involved the removal of hair, skin or blood without its parents' consent. In consequence of this, school children are so well protected by their teachers and other officials that it is often a very elaborate affair arranging for an experiment on a group of them. When a person comes into hospital, however, many investigations are made, and necessarily made, for direct diagnostic or therapeutic purposes, and patients expect a certain number of "tests". These are part of the hospital routine, and although patients have the right to refuse, it is extremely rare in this country for anyone to do so, and, as a matter of fact, many appreciate the attention. Hence, many experiments, even quite elaborate ones, can be made on patients, within the therapeutic routine of the hospital so to speak, without anyone thinking anything of it. Many experiments are made on this basis, and all help to define the effects of disease on function but the results seldom get recorded on the patients' notes. If the experiment is more elaborate and demands considerable co-operation, the investigator may feel it desirable to ask the patient for his "permission". It is often difficult for an investigator to explain the nature and object of his work to a non-scientific colleague and generally quite impossible to a patient. The investigator can only tell the patient in very general terms what his experiment will involve, explain the nature of the risks and ask for his co-operation. Experiments on children and infants are carried out on exactly the same basis except that parents have to be approached for permission, and the whole procedure becomes much more formal and tricky, for it is generally possible to size up a prospective subject before asking him for his co-operation whereas it is a very different matter to go up to an unknown parent on visiting day and make your request. It is still more difficult to approach a newly delivered mother about an experiment on her baby, even if this only involves a study of how it breathes, and the inclination to make the experiment without doing so is very great. Patients and parents, however, rarely refuse, and in my experience opposition to experimental work in hospital generally comes from colleagues under whom the patients have been admitted, and from the nursing staff who are, in general, antagonistic to research, especially on children, unless maybe it is being carried out by their own particular "chief". An experimental study always involves them in extra work the reason for which they do not fully understand and which often appears to them to run counter to their ideas about the comfort and care of the patient. They are on the whole satisfied with the knowledge of to-day. They forget that nothing in this world is static and that knowledge can be lost as well as gained. Research has made our knowledge great and can make it greater, but without research knowledge would fall away as it did in the Middle Ages. All our triumphs of to-day would be forgotten —they may be anyway—but without continuous research there would be nothing to take their place. Those who educate medical students and nurses should therefore emphasize to them the value of the experimental approach, and encourage them at some point in their careers to do something for the medical science of to-day and to-morrow by taking an active interest in experimental work.

No doubt the practice differs from one hospital to another, but the principles just outlined about "permission" seem to hold generally throughout this country. In some continental countries the position is rather different and the co-operation of the patient or parent is seldom sought and in some places it is generally assumed that it would be refused. This is an unfortunate state of affairs. A little thought shows that the whole position in this country depends upon trust. The patient trusts the staff of the hospital, and the investigator, knowing this, usually dispenses with the formality of asking for "permission", when his experiments simply involve procedures which

are the commonplaces of clinical practice, but he generally prefers to take the patient or parent into his confidence over anything more elaborate, and this is where his conscience and judgment become so important.

This seems a happy arrangement and one which we are fortunate to have evolved. Some other nations have not been so successful. The whole atmosphere of trust would be destroyed if patients had to be asked to fill in a printed form of consent for experiment as they are as a rule for an operation. I would feel happier, however, for the future, if patients could be made more aware that at some hospitals—the best hospitals—experimental work is carried out not only for the benefit of the immediate sufferers, but also for the benefit of mankind, and that they themselves owe incalculable advantages to work of this kind which has already been done on others; furthermore, that if they or their children are privileged to be admitted to these hospitals, they may be expected to co-operate. In the form given to patients on admission to one hospital I know, there is a small paragraph and the addition of a few words to it illustrates the sort of thing I have in mind. The additions proposed are in italics. "The hospital staff seeks your assistance in carrying out the hospital's duty to the community in the *investigation of disease and in the* training of doctors and nurses; if a member of the staff wishes to *make a special study of your condition or to* explain it to a medical student, doctor or nurse, it is hoped that we may have your co-operation."

Although it is legal to kill an animal without any vivisection licence and tissues can be taken immediately after death without any formalities whatever, it is extremely difficult to obtain fresh human tissues for experimental work unless they have been removed by a biopsy, for once a person has died a post-mortem examination may only be made with the permission of the next of kin or the person in lawful possession of the body (unless of course the coroner or the official referee under the Cremation Acts orders a post-mortem to be carried out to ascertain the cause of death). These manœuvres all take time during which the chemistry of the cells becomes completely disorganized, but, the law being as it is, it would, I feel sure, be unlawful to remove any part of the body for purposes of research immediately after the death of the patient without the previous consent of the nearest relative. This makes it very difficult to carry out many desirable investigations, and even the gross composition of the human body is still only known to us in very vague terms because of the legal obstacles which prevent a *bona fide* investigator from obtaining the complete body of a human being for analysis. With the co-operation of an anatomy school it can be done, and we have ourselves done it, but the removal for examination must not take place until forty-eight hours after death, and it is necessary to comply with other legal formalities. There is much more work to be carried out on the metabolism of fresh human tissues and on the chemical composition of the organs of whole bodies by people with the necessary interests and opportunities.

A great deal more might be said about the practice of experimental medicine, and its place in medical practice as a whole. Almost every statement I have made could have been greatly enlarged but it would be better for others to do this in the light of their own experiences. As I see it, however, the medical profession has a responsibility not only for the cure of the sick and for the prevention of disease but for the advancement of knowledge upon which both depend. This third responsibility can only be met by investigation and experiment, and from the nature of things it is always likely to remain the task of a few men and women specially gifted and/or trained for the purpose. Some of these people have in the past sacrificed considerable wealth for the mental satisfaction of their work. This may not have to be so in the future but all such practitioners have a right to expect the fullest co-operation from their medical colleagues, from nurses and other assistants, from hospital managements, from patients and relatives and from the community at large.

Section of Proctology

President—Sir HENEAGE OGILVIE, K.B.E., D.M., M.CH., F.R.C.S.

[*November* 29, 1950]

Chordoma of the Sacrum.—E. C. B. BUTLER, F.R.C.S.

History.—Male, aged 55. Eleven months ago he started to have pain over his sacrum. For three months he has had increasing constipation and straining on micturition.

18.8.50: *On admission.*—General condition good. Chest clear. Abdomen showed painless distension of the bladder half-way to the umbilicus. There was a large elastic swelling over the posterior aspect of the lower half of the sacrum attached to the gluteal muscles. Rectal examination showed a similar swelling bulging into but not attached to the rectum.

X-rays revealed extensive destruction of the lower part of the sacrum below the sacro-iliac joints. There was no new bone formation. An X-ray of the chest was clear and cystoscopy showed a normal bladder. A drill biopsy was performed. Report: Chordoma of the sacrum.

25.8.50: *Operation.*—Under a general anæsthetic the abdomen was opened and the intestines packed out of the pelvis. The patient was put into a steep Trendelenburg position. The rectum was mobilized posteriorly as far as the ano-rectal junction so that it was entirely free from the sacral tumour which had not penetrated through the pre-sacral fascia. The abdomen was then closed.

The patient was next turned on to his face in the scissor knife position. A large curved incision was made over the sacrum and the space between the growth and the rectum was entered by commencing the dissection below the coccyx. There was then no further chance of injury to the rectum.

The lower half of the sacrum was removed to the level of the sacro-iliac joints. Two prolongations of jellylike growth were found, one going upwards and the other outwards. These were removed with a spoon and the bony cavities were cauterized with pure carbolic. The whole operative field was then treated with X-rays in the theatre by Dr. Shanks, the rectum being protected by a lead shield. The wound was then closed with drainage.

Post-operative course.—The wound healed well, his constipation went and after his catheter was removed on the fifth day the patient was able to micturate normally. His bladder was no longer palpable. A full course of radiotherapy was given to the area of operation three weeks after the operation.

Pathological report (Professor D. Russell).—The specimen consists of the lower part of the sacrum with attached portions of gluteal muscle and the tumour which forms a mass measuring 7 by 6 by 5·5 cm. approximately in the concavity of the bone. The tumour appears to be covered anteriorly by peritoneum and on dissection replaces most of the bone. Its cut surfaces are friable, greyish white and mucoid. Hæmorrhages are present in places. Nodules of tumour tissue invade adjacent muscle.

Histology.—Sections prepared from (*a*) the anterior aspect of the tumour and (*b*) tumour with adjacent invaded muscle show lobules of small and large polygonal cells. The larger are conspicuously vacuolated (physaliferous cells). Large quantities of intercellular lightly hæmatoxyphil substance (mucin) separate the cells in many places. Similar material is often present in the cytoplasm.

Although a few nodules of tumour tissue are present in the adjacent connective tissue the appearances suggest a low order of invasiveness. The adjacent muscle shows marked atrophy from compression.

December 1950.—General condition good. No evidence of any local recurrence but there is still some difficulty with micturition and occasional nocturnal incontinence.

Discussion.—Chordomas of the sacrum are rare tumours, this is the fourth case to be treated at the London Hospital in the last fifty years. These tumours are very slow growing and usually present with either sacral pain, a swelling or disturbances of bowel and bladder.

Gentil and Coley reviewed 128 cases of these tumours in 1948, 7 of which came from the records of the Memorial Hospital New York. They came to the following conclusions: (1) The condition is very rare. (2) It occurs chiefly in males about the age-group 40–60. (3) Aspiration drill biopsy is the best method of diagnosis. (4) Metastases have been reported in 10% of cases. (5) The disease is of long duration and local recurrence after operation is the rule (GENTIL, F., and COLEY, B. L. (1948) *Ann. Surg.*, **127**, 432).

Abdominal exploration should always precede sacral excision so that the operator can decide at once if the rectum is involved; this approach also enables him to free the rectum from the sacrum early in the operation and so prevent its injury when the bone is being removed.

Total Colectomy for Carcinoma of Rectum and Hepatic Flexure, with Anastomosis of Small Intestine to Anus.—STANLEY O. AYLETT, M.B.E., F.R.C.S.

H. B., male, aged 71. First attended hospital December 16, 1948, complaining of passage of blood *per rectum* for eighteen months associated with increasing constipation in the last six months. During this time he had complained of a pain in the abdomen of a colicky type and had lost 3 st. in weight in the last three months.

On examination.—General condition fair. Teeth dirty. Abdomen: mass palpable in the region of the hepatic flexure. *Per rectum* 8 to 10 cm. from the anal orifice there was a hard craggy ulcer.

Treatment.—18.12.48: Full dental extraction and a biopsy of the rectal tumour which showed an adenocarcinoma.

7.1.49: Laparotomy—in addition to the carcinoma of the rectum a large carcinoma of the hepatic flexure was found (Fig. 1).

In view of the fact that a right hemicolectomy and an abdomino-perineal excision would probably have left the patient with a very wet, uncontrollable colostomy it was decided to perform a reconstructive abdomino-perineal excision in addition to the hemicolectomy.

These procedures were carried out in one operation (Figs. 2 and 3) the proximal end of the distal half of the transverse colon being brought to the surface as a colostomy. The patient was returned to the ward in good condition.

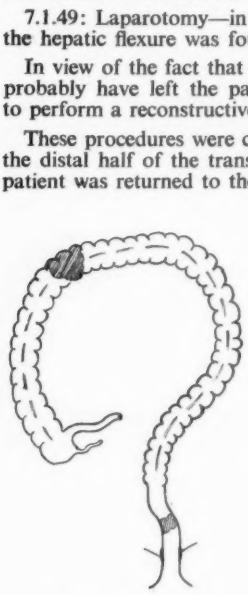

FIG. 1.—Carcinoma of rectum and hepatic flexure.

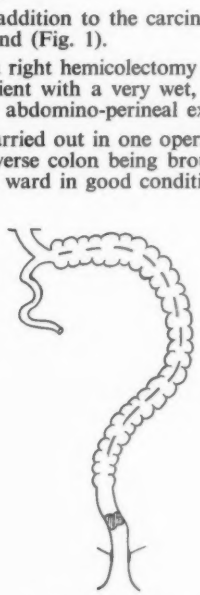

FIG. 2.—Stage I. Hemicolectomy.

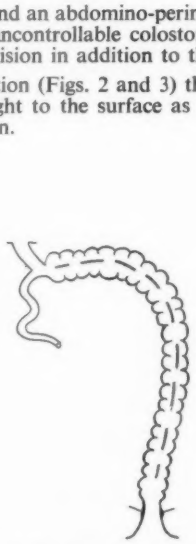

FIG. 3.—Stage II. Reconstructive abdomino-perineal excision.

FIG. 4.—Stage III. Anastomosis of ileum to anal canal.

Post-operative progress.—Four days after the operation liquid fæces leaked from the perineal wound in great quantity. Exploration of the perineal wound showed that about 6 in. of the colon anastomosed to the anal canal had sloughed. The patient's condition in the next few days began to deteriorate. It was decided that an attempt should be made to anastomose the small intestine to the anal canal, as likely to give the patient the best chance of survival.

On 25.2.49 this procedure was carried out. The abdomen was reopened and the small intestine divided close to its anastomosis with the transverse colon. The distal end of the small intestine was closed.

An incision was made in the pelvic peritoneum and the end of the small intestine pushed through this hole. The anal canal was then swabbed out by an assistant and with intestinal forceps passed through the canal, the free end of the small intestine was grasped and brought out to the surface. It was sutured to the peri-anal skin. The abdomen was then closed (Fig. 4).

Post-operative progress.—Recovery from the operation was uneventful. On discharge from hospital the patient was continent and remains so. He has his bowels open five to six times a day.

Non-Specific Stricture of Ampulla of Rectum.—HENRY R. THOMPSON, F.R.C.S.

History.—A male, aged 27, was first seen at St. Mark's Hospital on April 23, 1949, with an eight-year history of rectal bleeding and diarrhœa. He had been treated at the Royal Free Hospital from July 1941–June 1942 with a diagnosis of ulcerative proctitis. When seen at St. Mark's Hospital in April 1949 he was complaining of constipation, straining, flatulence, vomiting and attacks of abdominal pain with passage of blood and mucus.

Previous history.—An attack of infantile paralysis at the age of 2 years.

Examination.—Fit healthy-looking youth. Abdomen: the colon was outlined with fæces. Rectal examination: stricture palpable at the tip of the index finger, the lower edge of which was seen at 7 cm. from the anal margin and extended up to 13 cm. from the anal margin, the lower edge being situated just above the base of the prostate. The rectum above and below the stricture was normal.

Investigations.—Biopsy showed granulation tissue with no sign of tuberculosis or neoplasm. W.R. negative. Frei test (Lygranum) negative. Barium enema X-ray showed proctitis with stenosis of the rectum, but no other abnormality of the colon. X-ray of chest: slight infiltration of the left infraclavicular area suggesting a healed tuberculous focus.

Treatment.—After consultation with members of the surgical staff at St. Mark's Hospital, it was decided that the stricture should be dilated. Hegar's dilators up to No. 25 were passed over a period of seven months, at weekly intervals, until May 1950 with no permanent improvement.

Operation (May 31, 1950).—Abdominal resection of stricture with side-to-end colo-rectal anastomosis. This was done as a one-stage operation which subsequently proved to be an error of judgment; a defunctioning transverse colostomy would have been a wise precaution. Post-operative ileus, pelvic cellulitis and a degree of peritonitis developed which nearly cost the patient his life.

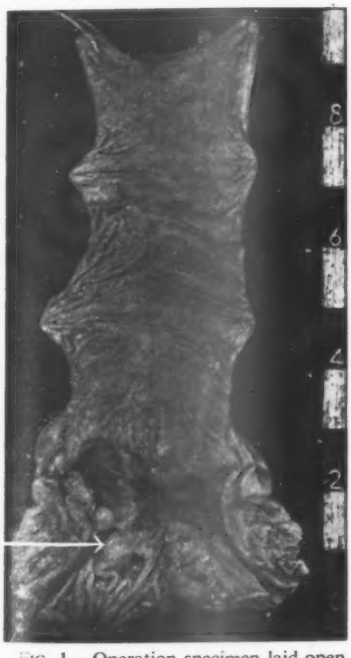

FIG. 1.—Operation specimen laid open through anterior wall, showing ulcerated strictured area in ampullary rectum. Rounded tumour (inclusion cyst) marked with arrow.

Present condition.—General health excellent, bowel action normal. He is now back at full work. His operation has resulted in loss of sexual function, which it is hoped is only temporary.

Pathological report (Dr. Cuthbert Dukes).—The specimen measured 9 in. (Fig. 1). A flat ulcer with shallow margins one inch across completely encircled the upper third of the rectum. There was 1½ in. of bowel below and 6½ in. above. The mucous membrane below the ulcer was nodular and furrowed in appearance. A round tumour ½ in. in diameter was situated close to the lower margin of the specimen. In the region of the ulcer the bowel wall was much thickened and the perirectal fat increased in amount.

Histology.—Sections through the ulcer show a bare area devoid of mucous membrane, the floor of the ulcer being composed only of the muscle coat of the bowel. At its margin there is some irregularity of the glandular epithelium and in the nodular and furrowed region below the ulcer the section shows several cysts containing mucoid material. Some of the cysts are lined by mucus-secreting columnar epithelium and have the appearance of implantation cysts. Several sections have been cut from the region above the ulcer, but these have revealed no abnormality.

Pathological diagnosis.—Chronic non-specific ulceration associated with inclusion cysts.

Polyposis Intestini: Treated by Total Colectomy.—W. B. GABRIEL, M.S., F.R.C.S.

A single woman, aged 27. Admitted into the Royal Northern Hospital on 12.6.50 under the care of Dr. Eliot Mackworth. She gave a history of diarrhœa for twelve months with up to 6 motions daily but no blood or mucus had been noticed. The motions were fluid and the rectum had to be emptied each time she passed urine.

On examination.—She appeared to be a healthy young woman apart from marked clubbing of the fingers and moderate pallor. Hæmoglobin proved to be 80%. Abdominal examination was negative. *Per rectum* an irregular nodular condition of the mucous membrane could be felt and sigmoidoscopy showed a diffuse polyposis. In the rectal ampulla the adenomas were so closely crowded together that no normal mucosa could be seen; in the rectosigmoid region a little smooth, pale, mucous membrane was visible in places between the adenomas.

A barium enema examination showed clear evidence of a diffuse polyposis involving the entire large bowel (Fig. 1).

Family history.—The position is complicated by the fact that her father, now aged 71, has married three times and has had children by each wife. The patient's mother was the second wife, and the cause of her death is not known; besides the patient she had four other daughters, now aged 33, 31, 28 and 26, each of whom has been examined; they are in good health and free from bowel symptoms; sigmoidoscopy reveals no evidence of polyposis and it is proposed to keep them under observation if possible. In addition the patient has one step-sister (aged 45) surviving from her father's first marriage, and another aged 24 from his third marriage: so far as is known these two are in good health but they have not been examined.

Operations.—In view of the patient's age, the recent onset of symptoms and the obvious impossibility of clearing the rectum by fulguration a total colectomy was advised and this was carried out in three stages as follows:

28.6.50: Terminal ileostomy.

19.7.50: Subtotal colectomy down to a colostomy stoma in the left iliac fossa.

6.9.50: Perineo-abdominal excision of the remaining recto-colic segment.

FIG. 1.—Case of polyposis intestini. Barium enema (evacuation film) showing extensive involvement of the entire colon.

Result.—The patient made an uneventful recovery from these three operations; she has put on weight and now looks very well. Her ileostomy is satisfactory and she manages it very well.

Pathological examination.—The severe degree of polyposis in this case is shown by the photographs of the two specimens removed. One early carcinoma was discovered by Dr. Cuthbert Dukes in the iliac colon (Fig. 2, A) and two similar group A carcinomas were found in the rectum and rectosigmoid (Fig. 2, B). These carcinomas were all of a low grade of malignancy.

Comment.—It seems fairly certain that any attempt at a conservative operation would have been a mistake in this case and a radical operation has given her an excellent prospect of permanent cure.

The case is of interest from the following two aspects:

(1) Examination of the operation specimens shows that three separate adenocarcinomas had already developed despite the fact that the patient had not observed any blood or mucus in her stools. (2) Up to the present time the patient appears to be the only member of her family afflicted with this disease.

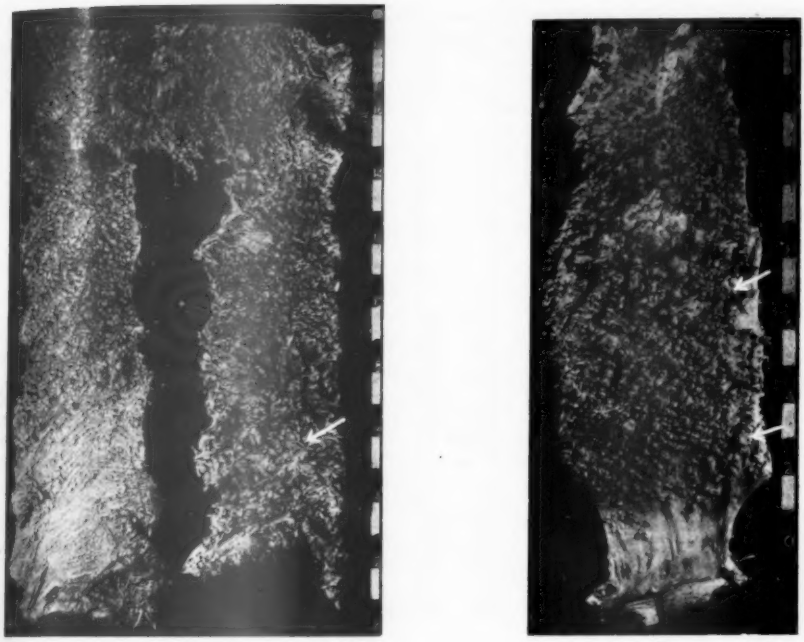

FIG. 2.—A, Subtotal colectomy specimen (cæcal end on the left) with one early adenocarcinoma (arrow) in the iliac colon, low grade, A case. B, Remaining recto-colic segment removed by perineo-abdominal excision. This specimen showed a dense clustering of the adenomas and in addition was proved to contain two adenocarcinomas (marked by arrows) both low grade, A cases.

Prolapsed Submucous Lipoma.—A. EMLYN WILLIAMS, F.R.C.S.

Mrs. B., aged 52. Admitted to the Hampstead General Hospital on September 30, 1950, complaining of a lump at the anus present for seven hours.

FIG. 1.

History.—The patient had suffered from chronic constipation for many years and this had been getting progressively worse during the past six months. For the past three months she felt "as if there was an obstruction in the rectum". The motions were formed and not altered in shape. A little mucus had been noticed but no blood. The day before admission she slipped and fell whilst lifting garden refuse to put on to a bonfire and felt pain in the lumbosacral region and across the left side towards the iliac crest. This persisted until the following morning when her second bowel action produced the lump at the anus and her pain was relieved.

On examination.—A smooth swelling 9 cm. × 6½ cm. × 6 cm. projected from the anus covered by smooth mucosa mostly pink in colour, but dark red in places (Fig. 1). It had a narrow pedicle at the anal margin. On sigmoidoscopy a fold of mucosa extended upwards from the tumour for about 11 cm. and apparently to the left lateral wall of the rectum. On the lumen side, the sigmoidoscope passed easily to 25 cm.

Treatment.—Under pentothal, nitrous oxide and oxygen anæsthetic the pedicle was transfixed with chromic catgut close to the tumour and the tumour excised with a scalpel. Inspection of the cut pedicle showed mucosa only.

Subsequent history.—Uneventful convalescence until the sixth post-operative day when she complained of acute lower abdominal pain followed by signs of diffuse peritonitis. At laparotomy a perforation was found in the proximal end of a long pelvic colon about 2 feet from the anus. The perforation in the upper sigmoid colon was 1 cm. in diameter and the transfixion stitch was seen in the œdematous underlying mucosa which had also given way. The affected loop of bowel was brought out as a temporary colostomy and the peritoneum drained. The patient recovered. Later, her long sigmoid loop together with the colostomy was excised and end-to-end anastomosis performed.

Histology (Dr. Cuthbert Dukes).—Submucous lipoma with considerable hæmorrhage into the tumour and œdema. "If not dead it is at least moribund!"

The following points of interest were discussed: (1) The high site of the tumour and the long distance it had travelled without producing signs of intussusception on clinical or sigmoidoscopic examination. (2) Perforation of the bowel after six days of symptom-free convalescence, despite transfixion close to the tumour.

A similar case has been described by Tuffier. This may have been due to invagination of the seromuscular wall at the site of this tumour. Such a condition was described by Sir John Bland-Sutton who noticed a "deep dimple" of the gut wall in association with some colonic lipomata; or it may have been due to the development of an intra-mural abscess which subsequently perforated.

(3) The moribund nature of the tumour.

These tumours have a poor blood supply which can easily be rendered precarious by traction on them. The section of this tumour serves to illustrate one of the features of colonic lipomata, namely, that they are liable to slough and be extruded spontaneously.

The following Cases and Specimens were also shown:

Carcinoma of Descending Colon with Co-existing Histological Appearances Simulating Crohn's Disease.—Mr. RONALD RAVEN.

Crohn's Disease of Whole of Colon.—Mr. STANLEY AYLETT.

Carcinoma Supervening on Crohn's Disease.—Mr. C. E. P. MARKBY.

Crohn's Disease with Massive Glandular Recurrence.—Mr. H. E. LOCKHART-MUMMERY.

Unusual Recurrence after Subtotal Colectomy and Ileo-sigmoid Anastomosis for Double Carcinoma of Colon.—Mr. J. C. GOLIGHER.

(1) **Basal-Cell Carcinoma of Anal Canal.** (2) **Unusual Local Spread of Rectal Cancer.**—Dr. CUTHBERT DUKES.

[*January* 10, 1951]

The Large Bowel and Its Functions

PRESIDENT'S ADDRESS

By Sir HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S.

NEXT to reproduction, the maintenance of the species, the most important business of any living creature is getting food, the maintenance of the individual. The business of dealing with the food after it has been got involves four processes, mechanical subdivision, digestion, absorption and excretion. The mechanism required to carry out these processes varies greatly with the diet and habits of the species. The carnivore has a difficult job to get his food, but a comparatively easy one in disposing of it. He subdivides it with his jaws and teeth, digests it in the stomach and upper half of the small intestine by enzymes liberated by the glands of those parts, absorbs it in the distal small intestine and the proximal colon, stores the small amount of residue that remains in a relatively simple distal colon, and has few enemies to hinder his leisurely evacuation. The herbivore has a very different life. His food is abundant, but he must eat it all day in enormous quantities. He subdivides the fibres and vegetable cell membranes by ceaselessly grinding between large molar teeth,

but his stomach churns the pieces still smaller, and sends it back into his mouth to be re-chewed. He provides digestive enzymes of his own, but has to depend largely on bacteria to break down the cellulose, and the gases that are produced by this constant hydrolysis keep him belching and rumbling when he is not chewing or defæcating. All the way through his alimentary canal he is trying to extract more nourishment from this food mass, and he needs an enormous colon to store it in its onward passage. Even when he has finished with it, he has by no means exhausted its food value as the sparrows that follow the cart-horse, and the fish that swim round the hippopotamus testify. He is defæcating at intervals all day, and, since he has many enemies from whom he has no protection but flight, he must be able to defæcate in a hurry.

The digestive system is the prototype of the modern factory. The owner thinks he is running the show, but his function is limited to ordering bulk supplies, and disposing of output and he has little control over the departments, and knows little of what goes on in them unless there is a strike. Each department carries out one stage in the process with which the factory is concerned. During working hours the doors are shut, and though it can communicate with those on each side of it, it does not usually do so. It passes on the material at a certain stage to the next department, and repeats the same job till the whistle goes. The doors that separate the four departments of the nutrition factory are the pharyngeal, the pyloric and the ileo-cæcal sphincters. In conditions of health each of these lets nothing through till it is ready for the next process, and lets nothing back once it has been passed through.

Functions of the Large Bowel in Various Mammalian Species

I have often protested, not against animal experiments, but against the facile way in which conclusions derived from these experiments are applied to human therapeutics. I mistrust in particular analogies drawn from experiments on the digestive system, for the material to be digested and the processes by which it is digested differ profoundly in each species. Most unsound gastric surgery is based on experiments on the dog, a creature whose stomach is designed to deal with enormous meals of raw meat, obtained at long intervals and bolted unchewed. The differences between the alimentary canals of different species is most marked in the large bowel, and though all mammals have the same complete segregation between the intestinal and colonic phases of digestion, the enormous length and diameter of the colon in the herbivore and the special development of the cæcum, point to a function differing profoundly from that of the carnivore and omnivore.

Man is omnivorous, and his teeth and his colon link him more nearly with the carnivora, or it would be safer to say distinguish him from the herbivora and separate him profoundly from the graminivora. His forbears were hardly beasts of prey, but they probably caught some of the smaller animals, and lived on eggs, birds, fish, nuts, grain and fruits.

In man the food arrives in the cæcum as a creamy fluid usually containing no macroscopic solid particles. The ileal efflux consists of 90% water, together with a small amount of the unabsorbed products of the digestion of proteins, fats and carbohydrates, as well as indigestible meat and vegetable fibres, bacteria, mucus and shed epithelial cells. In the cæcum and ascending colon some of the water and the remaining soluble products of digestion are absorbed, and the bowel content, by the time it reaches the proximal end of the transverse colon, has become recognizably fæcal; that is, it has been changed from a liquid to a soft solid mass, but the final fæcal consistency is not attained till the pelvic colon. From the transverse colon onwards the function of the large bowel appears to be to store the residue, to prepare the fæcal mass by abstracting more water, and to pass it on for evacuation. There is no further mixing in this onward passage, and after a melæna or a dose of charcoal it is not uncommon for a bicoloured stool to be passed, a sharp line dividing the normal-coloured portion from the black. The last function of the colon is defæcation, an act that is done naturally, reflexly, frequently and with evident enjoyment by most animals; but that in man and the dog has been so conditioned by early training to fit social customs and notions of decency and hygiene, that it is performed in guilty seclusion with considerable difficulty. Of the 500 c.c. that entered the cæcum, 100 c.c. have finally been discarded as a stool which still contains about 60% of water, and about half of whose solid content consists of bacteria.

The storage of the remains of a meal, for evacuation at intervals and at a convenient time and place, is one of the main functions of the large bowel, but in man and the carnivora, where the amount to be stored is small, not one of preponderating importance. In the herbivora, the colon serves not alone as a storehouse for the large amounts of only partly digested food residue that reach it from the small intestine, but as an incubator where bacteria continue the process of breaking down cellulose into soluble carbohydrates. In addition the colon of the herbivorous animal must prepare the final residue in a form suitable for instant evacuation. It is typical of the herbivora, particularly those who must

be prepared at any moment to seek safety in flight, that their motions are lying ready in round pellets that can be shed at the first note of alarm, or dropped while running at full speed. Any hunted animal who was obliged to strain, with arched back, closed glottis and a far-away look in the eyes, to expel the pultaceous contents of several feet of colon as a single elongated motion, as do the lion, the dog, and man, would be an easy prey to the hunter.

To extract nourishment from grass or leaves is a whole-time job, and even with the aid of mechanical grinding, digestive ferments, and bacterial action, the extraction is never complete. The fæces of carnivora are of little interest to other animals but those of the herbivora still contain abundant nourishment for other creatures, or even for the animals themselves.

In some instances the young are fed this way. The infant Koala bear, when it feels hungry, prods its mother's abdomen as it lies in her pouch, and forces out a motion which it proceeds to eat. In the rabbit the whole of the food eaten passes twice through the alimentary canal. The meal is taken into the fundus of the stomach, and thence passes down the small intestine into the capacious cæcum, where it is stored in the blind end and undergoes bacterial digestion. Some twenty hours later the cæcum contracts and its contents are rapidly passed down the colon to the anus, where they appear as "night fæces", white pellets that are smaller, moister and softer than the familiar black day fæces of the rabbit, and are coated with mucus. These night fæces are not passed, but are taken by the rabbit direct from the anus, swallowed without chewing, and stored in the cardiac end of the stomach while the main meal is eaten. When this meal has passed on to the small intestine, the night pellets enter the fundus of the stomach. The abundant bacterial protein they contain is absorbed in the intestine, the water is removed in the colon, and the residue is dropped as day fæces.

Defæcatory Habits in Animals

The fæcal mass is the daily record of the presence of an animal at a certain spot and a certain time. It is visible, odorous and abiding. It is the hall-mark of the species to the hunter, the visiting-card of the individual to another of the same species. It is natural therefore that defæcation should be the subject of customs and habits among animals, of rites and beliefs among men.

The native hunter knows the droppings of every creature, and he can tell from their character and temperature the age of the owner, whether he was serene or disturbed, and how long ago he passed by. Yet few animals conceal their droppings. The dick-dick, the smallest of the antelopes, always scratches a small hole into which he deposits his fæces, but the concealment is most ineffectual. The rhinoceros always defæcates in the same place, which is commonly recognized by hunters as a rhino-midden. Several rhinos may use the same midden. After defæcation they invariably kick out backwards to scatter the fæces, using powerful strokes of the back legs, which in time wear a couple of trenches in the ground. This scattering of the fæces, or of earth over the fæces, can hardly be an attempt at concealment, for it is a habit of attackers, particularly the cat tribe. The rhinoceros is herbivorous, but being heavily armoured and extremely stupid he attacks everything he can hear or smell. The impala, the most graceful of living creatures, leave their droppings in a communal place, but, apart from them, the group of antelopes, the horse tribe, the giraffe, the cow, the buffalo and the elephant defæcate anywhere. In animals living in a nest, a lair or a burrow, defæcation away from their home is an obvious hygienic necessity.

An important use of the excretion in the animal world is to convey messages, greetings and welcome to friends, warning to rivals. The only likely explanation of the incessant urination of the dog, that characterizes his wanderings but not his home life, is that as a pack-hunting animal he uses this means to allow his group to follow his movements. Solitary feeders, whether carnivora or herbivora, tend to confine their operations to well-defined territories, which they claim as their own and are prepared to defend against all rivals. Professor Hediger of Basle has made a special study of the organization of these territories among mammalia, and points out that, while among birds the claim to priority is acoustic (that first fine careless rapture of the thrush means no more than "you come into this garden and I'll peck your eyes out"), among mammals territory boundaries are usually marked by smell. Many creatures have special smell glands, placed on the head, or near the anus, which they rub against branches round the borders of their feeding grounds. The bear uses urine. The hippopotamus marks his territory with fæces, and has developed a special mechanism, a backward pointing penis and a fanned tail which he waves vigorously to scatter the mixture in as wide an arc as possible.

Defæcatory Habits in the Races of Mankind

Man, as soon as he learned to reason at all, must have been interested in his fæces, as the one part of him that was discarded daily. He must have noted the variations that accompanied ill-health, the looseness that followed a bellyache or an experiment with a

new food, the cessation that presaged death, and have observed that insect plagues and pestilences harried especially those that allowed fæcal soiling round their habitations. Early medicine is largely concerned with casting out evil spirits by emetics and purges, and early tribal law with hygienic rules for the disposal of excreta.

The instinctive reaction of man to his own excreta and their odour is one of disgust, a feeling that the excreta of domestic animals, which also smell, but differently, do not arouse. All the African races abhor fæces and everything connected with them. The native African, however poor and however menial his occupation, will never clean a lavatory, a task that in Africa must be undertaken by Europeans or Indians. The Bantu races indeed have a horror of defæcating in a house at all, and regard the European practice of building lavatories inside their homes as something unspeakably repulsive. They can hardly be persuaded to use these foul contrivances, even in hospital, and when they do they stand on the seat and defæcate in the squatting position, which is normal to all native races, and having finished drop the stone they have brought to clean themselves into the basin, with the results to the seat and the drain-pipes that can be imagined. The Mahommedan is particularly obsessed with the need to avoid fæcal soiling and will always use his left hand for cleaning; he will offer this hand to another only as the deadliest insult known to him. Asiatics usually go to the fields, and take a bowl of water to cleanse themselves. The tribal African when ill brings a chicken to his medicine man to buy a purge or an enema. The society matron lays in stores of health salts claiming to give "inner cleanliness", pays her weekly visit to a colon parlour, or spends her yearly vacation at a Health Clinic.

Experience has taught those races who have learnt to profit by it two things about fæces, that they have a high fertilizing value, and that they may spread disease. The Chinese, who have contributed more to world culture (as distinct from material progress) than any race, distribute their excreta over their fields, after much thought and discussion, according to the needs of their crops for manure. The same habit among the Maltese led to a serious outbreak of amœbic dysentery during the late war.

Many native races on the other hand developed the latrine system at a time when the habits of Europeans were indescribably filthy. The first explorers to reach New Guinea found that all villages had pit latrines 30 to 40 feet deep, too deep for hookworms to get to the surface or for flies to get down. Captain Cook remarked on the cleanliness of these savages at a time when the inhabitants of London and Paris were emptying their slops out of the windows into the street below. The Maori villages had communal latrines some distance away, often placed on the edge of a cliff and concealed by creepers. Hygienic practices, such as those outlined in the Old Testament, develop slowly over the centuries, and are lost when the tribal organization that created them breaks up. The Elizabethans were probably much less fastidious than the Ancient Britons. The Southern European transplanted to Africa, sheds the cleanly habits of civilization and fails to acquire those of the native.

The History of the Enema

When we realize that man has associated his motions with his health from dim antiquity, it is not surprising to find that the oldest therapeutic device in the world is the enema. There is to-day no race so primitive and so sequestered that rectal lavage is unknown to them. Herodotus tells us that the ancient Egyptians maintained their health by giving themselves an enema at every cycle of the moon. The Ebers papyrus gives prescriptions for enemata and directions for giving them. Pliny goes further and says that the Egyptians learned the habit from the Ibis, which stands on the banks of the Nile and "washes the inside of his body by introducing water with its beak into the channel by which our health demands that the residue of our food should make its exit". Hippocrates advised enemata of honey and ox-gall, both much more up-to-date prescriptions than those in vogue thirty years ago.

The methods used to-day for giving enemata by the primitive races are very similar. All are remarkably traumatic, and the number of unrecorded deaths in the wilder regions from perforation of the pouch of Douglas probably exceeds those from duodenal perforation in the world's capitals. The commonest device is a cow's horn, with the tip sawn off or drilled. The patient sits in a swiftly running stream, inserts the tip of the horn into his anus, and allows the water to flow in under pressure; when he feels full he withdraws the horn and expels the contents of his bowel into the stream. Alternatively the horn may be filled with some herbal concoction, usually very hot, and, after inserting the point, the medicine is blown in by the witch doctor or a friend. Hollow reeds were also used, particularly for children. A common form of enema syringe described by Hippocrates but still used to-day in many parts of the world, is an animal bladder (usually that of a pig) lashed to a hollow reed: this instrument is filled by gravity and emptied by manual pressure.

The syringe was first described by Mario Gatenaria in the fifteenth century and was developed by de Graaf, who first gave it a curve, and finally designed an instrument fixed on a stool which the patient was able to manipulate himself. In the seventeenth century the enema became both popular and fashionable, following the lead of Louis XIV who used it frequently. In France at this period the enema became so common that it was a familiar subject for cartoons, and was introduced by Molière into his play "Le malade imaginaire". Every well-established house had an enema stool by the fireside, where it was used with complete openness by everyone in turn.

Where do we stand to-day? The old taboo that the large bowel and its contents are unclean remains the fundamental belief of the populace, one on which the fortunes of the manufacturing chemist, the nature healer and every quack, qualified and unqualified, are founded. On every hoarding we read "inner cleanliness comes first", on the back of every bus we are abjured "when nature forgets, remember!" In our newspapers we are addressed with affectionate concern "Don't let constipation rob you of your priceless gift of health".

It is natural that this sort of appeal is most likely to succeed among the lower intelligence grades, and a very good index to the standing of a journal is the number of laxative advertisements it contains. A survey on self-medication undertaken during the war revealed that purgatives greatly outnumbered all other self-prescribed and self-administered remedies, and that the amount of self-medication varied inversely with the education and intelligence of the group under investigation, but colon hysteria is not limited to the poor in purse or in wits. Colon parlours, nature cure homes and Continental clinics flourish on the patronage of wealthy and aristocratic coprophobes.

Surgeons cannot exonerate themselves from guilt. Lane, the founder of modern orthopædics, when he forsook bones for bowels, started a racket that is not dead yet. Those who knew him know that he was entirely sincere, and when he spoke of "the large bowel or cesspool of the intestinal tract" he believed that he was showing the human race the pathway to renewed health. Many of those who followed his lead were equally sincere or at any rate were mesmerized by his burning faith into a belief that the colon is evil. But colectomy for "stasis" and the colopexy which followed it and still survives to some extent, must be remembered among the more discreditable adventures of surgery.

The Modern Outlook

The modern outlook is to accept the colon as a normal and necessary part of the human digestive system, designed by evolution to fit the needs and the dietary of *homo sapiens* as a salvage and disposal plant, sifting the residue of digestion for anything that can usefully be kept and passing the rest on. We doubt the existence of constipation as a disease, but look on it rather as a colonic laziness that springs from mental laziness and that can be corrected by effort. We do not accept a rigid time-table, but think that if a man's bowels do not work at the usual time it is because they do not want to do so, and as soon as they do they will: till that time comes it is better to carry the stigma of constipation than to offer the insult of purgation. We believe that all aperients, by hurrying the natural procession and hindering the absorption of nutriment and water, increase the bacterial pabulum and therefore the bacterial population of the bowel. We hold that the only people who are harmed by constipation are those who believe the advertisements and develop a lavatory neurosis.

Have we perhaps overdone our negation? Are we right in assuring ourselves that the colon can do no wrong? The bacterial inhabitants of any particular colon have not been selected by their host, but got there by chance and stayed there by their ability to subsist on what nourishment reached them, to survive in competition with others using the same board and lodging, and to withstand the antibodies and the phagocytes of their host. They are not a standard assortment but their grouping may be changed by any fresh entrant or by any change in diet or habits. Very few people who served in the Middle or Far East during the recent war have returned with the same bowel habit which they had before. Even though they never suffered from clinical dysentery, the majority have looser stools and more frequent evacuations than they had before and most feel better for it. During the German occupation of the Channel Islands the inhabitants lived on meagre fare. They lost weight and they had several semiliquid motions a day but they felt well. During this time appendicitis, asthma and duodenal perforations vanished. With liberation the once a day habit returned and appendicitis once more became common. One island doctor who suffers from erythema multiforme has never passed a year free from an attack with the exception of these four years of altered colon habit. Striking examples of the way in which a change of colonic flora may affect health are constantly coming to light. A year ago a man of 65 was admitted to hospital suffering from intestinal colic and distension. Since a resection seemed probable he was put on a course of Sulfathalidine and vitamin K.

He escaped operation and his psoriasis which had been present in large patches in both thighs for forty years and had resisted all the wiles of the dermatologist, cleared up entirely and has not reappeared. That a diseased colon may give rise to distant lesions is well known: the dermatitis that may be seen in ulcerative colitis clears up as soon as the colon is removed, usually after ileostomy alone; the arthritis that accompanies amœbic dysentery is cured by elimination of the protozoa.

The Physiology of Normal Defæcation

The innervation of the large bowel resembles that of the rest of the abdominal part of the alimentary tract, the sympathetic system stimulating movement, the parasympathetic system inhibiting it. Alvarez' law of the intestinal gradient applies also to this part of the intestine, the upper parts having greater tone and a greater rate of rhythmical contraction than the lower parts. The right colon churns and mixes, the left as far as we know undergoes only two or three contractions a day. These movements, when they are going smoothly, are not represented in consciousness. It is only in the last function of the alimentary canal, as in the first, that conscious participation in an act that is largely reflex is resumed.

Normal defæcation has two aspects, the call to defæcation and the act of defæcation. Some stimulus, that may be emotional but is never voluntary and is usually some physical circumstance such as a hot drink, the first meal of the day, or in many the change from the horizontal to the upright posture, originates a wave of peristalsis in the distal colon that forces some fæcal matter into the rectum, and, by distending it, starts the defæcation reflex and the desire to accomplish defæcation. The act is performed by taking a deep inspiration to depress the diaphragm, closing the glottis to hold it down, flexing the spine to approximate the thoracic margin to the pubis, and contracting the abdominal muscles. The effect of these actions is to depress the hepatic and splenic flexures and transverse portions of the colon, to shorten the ascending and descending portions and to subject the whole to a greatly increased intra-abdominal pressure. At the same time the sphincters are relaxed, and the whole distal colon undergoes a wave of mass peristalsis, emptying its contents from the splenic flexure onwards into the rectum. The act is finished by contraction of the levatores ani drawing the still relaxed sphincters up over the tail of the fæcal mass.

This act of defæcation involves two mechanisms, the involuntary and the voluntary, and each mechanism has two opposing functions, the prevention of evacuation when it is not timely and its facilitation when it is.

There is a reciprocal relationship between the rectal walls and the internal anal sphincter which is the lowest part of the circular muscle coat of the rectum. The internal sphincter is normally in a state of tone, sufficient to guard against the expulsion of contents when they are fluid or gaseous, or when the intra-abdominal pressure is suddenly raised by coughing, sneezing or abrupt movements. The sphincter relaxes when the rectal walls contract in response to the defæcation reflex. The nervous mechanism for this reciprocal innervation appears to be solely in the peripheral nervous plexus of the rectal wall. Thus automatic rectal continence depends upon the plastic adaptation of the rectal walls to the enlarging fæcal mass, and when the walls are stretched to a certain point, or at more than a certain speed, they are stimulated to contract while the sphincter relaxes. This automatic defæcation occurs after transection of the cord in the lumbar region or after destruction of the lumbar and sacral cord. The preservation of the reflex centres in the sacral portion of the cord brings, according to Denny-Brown and Graeme Robertson, "a progressive character and greater fusion to the rectal contractions". Reflex defæcation in the intact animal can be suppressed by voluntary control or stepped up by voluntary effort into the full act of normal defæcation.

Voluntary control depends upon the contraction of the external sphincter ani. This remarkable muscle, the sentinel of social security, has properties belonging to both voluntary and involuntary groups. Its fibres are striated and they contract in response to volition; but they retain their microscopic structure and their reaction to electric stimulation after section of their nerve supply, and they contract as part of the protective reflex when the abdominal pressure is suddenly raised.

Control means the curbing of something that is about to take place, and therefore implies the knowledge of such an impending event. The awareness of impending defæcation implies two types of sensation: (*a*) The sensation of distension of the muscular coats of the rectum which starts the unconscious defæcation reflex and also gives the conscious warning that the trigger has been pulled. (*b*) Recto-anal sensation, which gives information on the nature of the material about to be expelled, whether it is solid, liquid or gas.

With this information available, the external sphincter is brought into action to restrain the passage of fæces or flatus till an appropriate moment.

Surgical Applications of Physiological Knowledge

So-called conservative resections of the rectum are performed: (1) For inflammatory lesions, chiefly ulcerative colitis. (2) For non-malignant neoplasms, papillomatosis or villous tumour. (3) For malignant tumours considered by the surgeon to be sufficiently early and sufficiently high to justify the retention of anal defæcation.

These conservative resections have had a bad press because they usually give imperfect control, and because, when performed for cancer, they are often followed by local recurrence. The control is imperfect because surgeons are apt to regard defæcation as an anal rather than a rectal function, and control as the simple affair of a purse string pulled by the cerebral cortex. Without the local nervous mechanism in the rectal wall, involuntary control is destroyed. Without the awareness of rectal distension voluntary control is illusory, and without the ability to distinguish fluid from solid it may be surprised. Satisfactory function after conservative resection is only possible therefore if the rectal walls are preserved, and if some portion of the sensitive ano-rectal mucous membrane remains.

It follows, first, that there is no place for conservative resection in cancer unless the growth is well above the pelvic floor. And secondly that in conservative resection for non-malignant conditions the rectal wall with its contained nervous plexus must be preserved. Submucous resection of the rectum in non-malignant conditions has been advocated and practised by Mark Ravitch and by John Devine, whose article will shortly appear in *Surgery Gynæcology and Obstetrics*.

Conclusion

What lessons may we, as proctological surgeons, derive from this review?

(1) First we must remind ourselves, our colleagues, our patients, and the public, that the large bowel is a normal and necessary piece of apparatus, and must wage unceasing war on coprophobia and the blood-suckers who prey upon it.

(2) Secondly we must continue to study the interrelation between the mind and the colon. We know that under conditions of stress barium may appear in the transverse colon ten minutes after it has been swallowed. We know that mental stress long continued appears to be a causative factor in many cases of ulcerative colitis, and may, as I believe, be a contributory factor in Crohn's disease. We know that the exteriorized colon can be trained to behave by intelligent discipline, and that the disordered mind and disordered colon of the neurotic play upon each other.

(3) Thirdly in discussing resections for disease we should consider the large bowel as a whole. A healthy colon is an asset, a bad colon a liability. The colon changes its function progressively; large sections can be removed without grave loss, and on the whole the distal or storage part can be spared more easily than the proximal or digestive part. The ileo-cæcal sphincter should not be sacrificed lightheartedly, for its removal throws two entirely distinct departments of the digestive mechanism into one.

(4) Lastly we must remember that normal defæcation is essential to health and happiness, and that abnormal defæcation through the normal aperture may be a fate considerably worse than well-trained colostomy.

My review has touched upon the comparative anatomy and physiology of the large bowel, and the elaborate overlay of mystery, folklore, and old wives' medicine that has grown round that very useful organ, but it has also brought us to the very foundation of medicine. The one sure basis of sound medicine is the belief that nature is always right, and that the duty of the physician is to study what she is doing, to help her in the very few instances when she is in difficulty, but never to nag or interfere with her while she is doing a job that she knows far more about than we do. We must accept as axiomatic that all parts of the body are perfectly designed for the job they are intended to do, for their design is the result of improvements and adaptations over millions of years on the original blueprint, and each modification has been produced to meet some functional need. The workings of evolution have been directed towards function rather than form, and we find therefore the greatest similarity among different species in those parts which perform a similar function, the greatest difference in those whose function differs. All mammals see; their eyes are very much the same. They all hear; their internal ears are almost identical except in size. They all run about; their femora, tibiæ, humeri and radii are built on the same basic pattern, from the giraffe to the dachshund; but they run on very different surfaces, so the hand and foot of man, the most primitive of all mammals, have been modified into the claws of the mole, the pad of the hare and the hoof of the horse. They differ most of all in their diet, and therefore we find the greatest modifications in the teeth, the stomach, and the large bowel.

But all these structures are fundamentally right; and we interfere with them at our peril. As proctologists we may translate the old adage "Mens sana in corpore sano" into "normal defæcation brings a contented mind" and normal defæcation in turn comes from equanimity and common sense. "Sanum e sana mente nascitur corpus."

Section of the History of Medicine

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The Early History of Radium in London

By C. E. IREDELL, M.D., M.R.C.P.

THE introduction of radium into London was attended by several unusual circumstances and as the number of those who were associated with it is fast diminishing, I thought it might be of some interest to deal with this subject while it is still fresh in living memory.

When it is remembered that this element was discovered by Professor and Mme Curie in Paris it is hardly surprising that the earliest medical use of it was in France. In England early in the century King Edward VII developed a rodent ulcer on his cheek. The various members of the medical profession who held office in the Royal Household were called in to see it, and as a result it was decided that he should have treatment with zinc ionization—a treatment which was then new—and that it should be administered by a well-known electrotherapist. It might be thought that in such a simple process as this nothing could go wrong. Unfortunately, however, on this occasion the unexpected happened. The King was in the habit of wearing a locket and chain round his neck, which had been given him by Maximilian, Emperor of Mexico. Sir Frederick Treves, who told me the story, was unable to explain what happened from an electrical point of view but there was no doubt that His Majesty received a severe electric shock—through the chain. He was understandably annoyed. The electrotherapist was never received again and it was clearly impossible to continue the treatment.

At that time Sir Malcolm Morris was dermatologist to the King and had always kept in touch with medical developments on the Continent. Radium had already been used in London in small amounts—usually about £20 worth in such cases as rodent ulcers, warts and nævi—in a desultory manner and with varying results. Sir Malcolm found that in Paris by using much larger quantities of radium (ten times or more than that usually employed in London) far more important and definite results were obtained. He found out all the necessary details for treating a rodent ulcer and bought 22½ mg. which were spread over a flat metal surface 3 cm. square, at a cost of £362.

All this was simple, but a very real difficulty arose when the doctors had to decide on a method of applying the radium to the ulcer. The King was impatient of any form of constraint and it was recognized that even if the radium were applied to the ulcer he would probably remove it before the period of cure was finished. So the radium was fixed to a pair of spectacles and this somewhat cumbersome combination was given to the King who was to put it on and read *The Times* for twenty minutes. The treatment succeeded admirably. The ulcer got well and no recurrence took place, a result that even to-day would be considered satisfactory.

The success of this treatment brought the possibilities of radium to the notice of one of the King's surgeons, Sir Alfred Fripp, who suggested to Sir Cooper Perry, the Superintendent, that they should be investigated at Guy's. Consequently I was sent to Paris and visited several hospitals—amongst others the Beaujon, the St. Antoine and the St. Louis. The results on cases of inoperable malignant disease were remarkable—quite different from anything that I had ever seen at Guy's or elsewhere, and I therefore paid a second visit to Paris six weeks later to exclude any possibility of my having been mistaken. In many of these cases the disease was deep to the surface of the skin, and in these certain precautions were necessary.

It had been discovered that radium gave off three different kinds of rays known by the Greek letters Alpha, Beta and Gamma. The Alpha and Beta rays preponderated in quantity but had comparatively little healing properties. On the other hand the Gamma rays, which formed only 3% of the whole radiation, appeared to destroy cancer cells without doing any harm to the healthy cells around them. The Alpha and Beta rays were unable to penetrate a piece of lead 1 mm. thick. The Gamma rays penetrated lead of this thickness but in passing through it set up secondary radiation which had an irritating effect on the skin and in some cases appeared to increase the growth of cancer. To protect the skin from this secondary radiation 20 pieces of paper, 4 pieces of lint and 2 pieces of gutta-percha tissue covered the lead over the radium which was then applied for forty-eight hours.

Longer applications were liable to produce unpleasant effects such as malaise and a rise of temperature. It was particularly important to avoid these, as when produced a recurrence was more likely to occur.

As a result of my report the Governors of Guy's purchased a radium applicator similar to the one already mentioned and it was at once put into use. It soon became an object of great interest and was seen and examined by large numbers of people. Among them was King George V, at that time Prince of Wales. On one of his visits to Guy's he was told that a large radium applicator had recently been purchased by the Governors. He had evidently heard of it, for he replied, "Yes, I want to see it". On the back of the applicator was the figure "500,000", which referred to its radio-activity, and he asked what it meant. Of the hundreds of laymen to whom the radium was shown he was the only one who asked this question.

King Edward VII's interest in cancer and radium was stimulated not only by its effect on his ulcer but also by the fact that his brother had died of this disease, and he asked his two friends, Lord Iveagh and Colonel Ashley, each to give £50,000 to found an Institute for Radium Treatment. This was carried out. But the work done, though excellent, was much hampered by the fact that no provision was made for the treatment of in-patients.

Not long after this, in May 1909, I received a visit which was of great interest to me personally and which might have led—had things turned out differently—to London becoming the world centre for the investigation for the cure of cancer. My visitor was Dr. James Douglas of New York who came with Dr. Perry of Folkestone and Dr. Telfair, his family physician. We had a discussion on radium and allied subjects, and I gave them an account of the work we were doing at Guy's and of what I had seen in Paris. They visited Guy's and then went to Paris with a list of the hospitals I suggested they should visit. I had not expected to see them again as the facilities for work with radium were much greater in Paris than in London, but at that particular time it happened that there were some cases at Guy's which showed in a very striking manner how much good could be done with radium.

Before coming to England he had made inquiries in New York and as a result wrote to Dr. Perry: "We are going to the only place where we understand there is both experience and radium . . . London." While later Dr. Bainbridge wrote: "Many workers have been particularly dissatisfied with radium because they have endeavoured to use low activities and small quantities, but in France and in Guy's Hospital, in London, where they use larger amounts, the best work has been done." Dr. Douglas's visits on this side of the Atlantic very largely confirmed this.

By this time he had been joined by Dr. James Ewing, the pathologist and cancer expert, and he decided to make Guy's the centre of his activities in trying to find a cure for cancer. With this object I accompanied him on visits he paid—to Dr. Lazarus Barlow at the Middlesex Hospital Cancer Research Laboratories, to Professor Strutt at the Royal College of Science, to Sir Ernest (afterwards Lord) Rutherford at Manchester, to mention only some of them. The latter, when asked, at once agreed to recommend an expert physicist to equip and start a Laboratory to investigate from a scientific point of view the effect of radiation on living tissues. I believe this was the first Biophysics Laboratory to be instituted.

Dr. Douglas did everything possible to facilitate the development of cancer research. One small instance may illustrate this. I happened to say in his hearing that I wished I could get to know what was being done in Brunswick with radium. The idea that he would go himself never occurred to me but he went off next day and came back a few days later with the information I wanted. He was then 74 years of age. In addition to the laboratory he provided more radium and founded a studentship of £300 a year.

Dr. Douglas soon came to the conclusion that in order to attain his object investigations would have to be carried out on a much larger scale, and then difficulties arose. He made a great point of visiting and seeing for himself what was being done for cancer at different hospitals. In Dr. Ewing's words: "He had first-hand information from all existing radiation centres and his decisions were based on very wide and competent investigation." On the other hand the Superintendent and the Dean who represented Guy's in the matter never once went into the Radium department to see what was being done there. Dr. Douglas did not know this but it is hardly surprising that difficulties arose in spite of the fact that he agreed to almost every suggestion made to him. For instance, the Superintendent and the Dean wanted research to be carried out on mice in a Pathological Laboratory while Dr. Douglas, though he agreed to this, would have preferred investigations to be made on patients suffering from cancer.

Ultimately he told me that he had come to the conclusion that Guy's was not interested in the cure of cancer by means of radium and he did not propose to do any more for it. He continued to pay for the studentship and other commitments he had entered into and for years took an interest in all that was being done at Guy's, and for several years we corresponded. In December 1913 he wrote to me: "I hope you are making some progress, though it does not seem to me that the atmosphere is very scientific and that most of the staff—not

however including Mr. Arbuthnot Lane—are inclined to jog along in the old-fashioned way. You have a fine big pathological building but there seemed to be very few workers in it." It may be of some interest to say a few words here about Dr. Douglas, who was the grandfather of Mr. Lewis Douglas, lately American Ambassador to Great Britain.

He was the son of a Scots doctor who after qualifying in Edinburgh and London migrated to Canada where he became the leading surgeon. He was unfortunate enough to get into difficulties over some mining properties at an age when he could hardly hope to extricate himself from his commitments, and his son, Dr. James Douglas, therefore made himself responsible for them, threw up the professorship of chemistry which he then held and went into business, becoming one of the richest men in the States. He spent £250,000 on the Memorial Hospital, New York and, in addition to this, vast sums in other directions. This was the largest sum spent on cancer research up to that time and it should really have come to Guy's.

Leonardo da Vinci, and the Movement of the Heart

By K. D. KEELE, M.D., M.R.C.P.
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IN October 1517 Cardinal Luis of Aragon, with his Secretary, paid a visit to Leonardo da Vinci in his house in one of the outlying parts of Amboise. Here they were shown various pictures, and the Secretary notes of the visit:

"This gentleman has written of anatomy with such detail showing by illustration the limbs, muscles, nerves, veins, ligaments, intestines, and whatsoever else there is to discuss in the bodies of men and women, in a way that has never yet been done by anyone else. All this we have seen with our own eyes; and he said that he had dissected more than thirty bodies both of men and women, of all ages. He has also written of the nature of water, of diverse machines and of other matters which he has set down in an infinite number of volumes all in the vulgar tongue, which if they should be published will be profitable and very enjoyable" (MacCurdy, 1938, quotation).

The "infinite number of volumes" referred to were taken by Francesco Melzi who treasured them to the end of his life, that is to say for fifty years until 1570, in his villa at Vaprio near Milan.

The anatomical manuscripts through Pompeo Leoni found their way to Spain. The next we hear of them is their discovery at Windsor when Mr. Dalton, the King's Librarian, informed William Hunter, who in 1784 requested permission to examine them. He comments:

"I expected to see little more than such designs in anatomy as might be useful to a painter in his own profession. But I saw, and indeed with astonishment, that Leonardo had been a general and a deep student. When I consider what pains he has taken upon every part of the body, the superiority of his universal genius, his particular excellence in mechanics and hydraulics, and the attention with which such a man would examine and see objects which he was to draw, I am fully persuaded that Leonardo was the best anatomist at that time in the world."

Though William Hunter hoped to publish engravings of these anatomical figures, he died before this was accomplished, and not until 1916 was such a publication completed.

Leonardo's known manuscripts consist of over 5,000 pages, the largest part of which is on mechanics. There are some 190 pages on anatomy of which about 50 or 1% of the whole are on the heart.

Leonardo's approach to anatomy was essentially that of an illustrator. As comparison with the anatomical figures of his day makes clear, he was the first to make naturalistic representation of the organs of the body, including many of the heart.

With regard to physiology his approach was governed by three main lines of thought. First, he accepted the fundamental Galenic principles but stripped them as far as he could of all their occultism. Secondly he substituted for the occult powers of Galen four mechanical powers:

"Force with material movement and weight with percussion, are the four accidental powers in which all works of mortals have their being and their end" (Arundel MSS. No. 263, 151).

"I have drawn up the rules of the four powers of nature without which nothing through her can give local movement to these animals" (Quaderni d'Anatomia 1, 1).

Leonardo considered that it is on the basis of friction produced by these powers, that heat, the basis of life, emerges. He devoted much study to the phenomenon of friction with heat production, in solids and liquids. The relationship of heat to life is made clear in his statement:

"Where there is life there is heat; where there is vital heat there is movement of the watery humours" (Codice Atlantico, 80).

In Leonardo's view the essential function of the heart was to produce the heat of the body. This it did by friction of the blood inside it, which was thrown from auricles to ventricles, rather like milk in a churn.

The third great principle of Leonardo's physiology was the application of the analogy between macrocosm and microcosm.

"Man has been called by the ancients a lesser world, and indeed, the term is rightly applied, seeing that man is compounded of earth, water, air and fire, this body of the earth is the same. And as man has within himself bones as a stay and framework for the flesh, so the world has the rocks which are the supports of the earth; and as man has within him a pool of blood wherein the lungs as he breathes expand and contract, so the body of the earth has its ocean, which also rises and falls every six hours with the breathing of the world. As from the said pool of blood proceed the veins which spread their branches through the human body, in just the same way the ocean fills the body of the earth with an infinite number of veins of water" (MS. A. 54).

A subject to which Leonardo gave great attention was the number of ventricles of the heart. According to Galen, and accepted by Avicenna and Mondino, the heart consisted of two ventricles into which the vena cava and arteria venalis (i.e. the pulmonary veins) opened by dilated mouths. Small auricular appendages were recognized, and thought to accommodate superfluous blood and air. Leonardo himself attached great importance to the discovery that, as he said:

"The heart has four ventricles, that is to say two upper ones, called auricles of the heart, and below them two lower ones called the right and left ventricle" (Quaderni d'Anatomia **2**, 17).

He writes extensively on such problems as:

"Why the auricles on the ventricles of the heart were made" (Quaderni d'Anatomia **2**, 3); "whether nature could make the right ventricle larger and abandon the upper ventricle or not" (Quaderni d'Anatomia **1**, 4). He discusses the Galenic contention that there are only two ventricles under the heading "reply to the adversary against the number of ventricles, saying there are two and not four". And he devotes a whole page of manuscript proving "how the upper ventricles are not one and the same with the lower" (Quaderni d'Anatomia **1**, 3).

Corresponding with this discussion are drawings which show how his appreciation of the anatomy of the auricles, or atria, developed, culminating in the illustration shown in Fig. 1. This was drawn probably about the year 1513 towards the end of his life.

Much of Leonardo's discussion is devoted to the subject of the function of the newly discovered auricles or upper ventricles. This he considers to consist of contraction, throwing the blood into the lower ventricles, and dilatation as they receive the blood thrown back into them from contraction of the lower ventricles on each side. In this way, the blood was heated

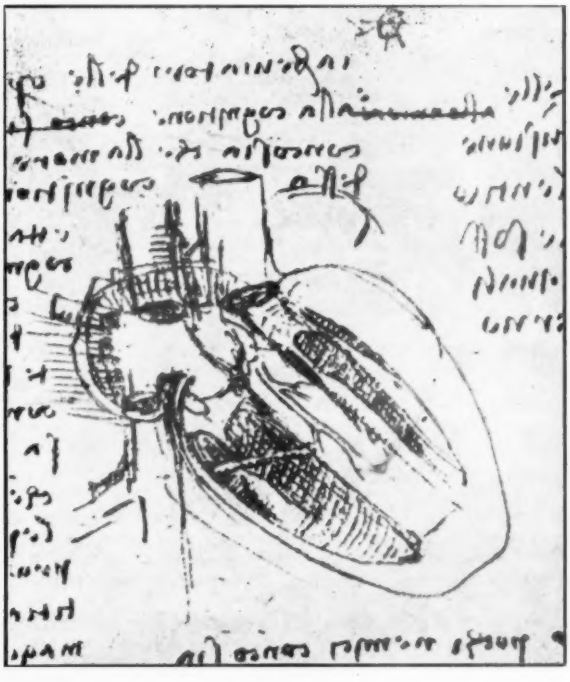

FIG. 1.—Dissection of the heart displaying the right atrium, right ventricle with moderator band, the anterior descending branch of the coronary artery, and the left ventricle with papillary muscles and cordæ tendinæ attached to the aortic cusp of the mitral valve (Quaderni d'Anatomia **2**, 14).

before its distribution through the vessels, both arteries and veins, to the organs and tissues of the body.

Though Galen and his successors had considered the heart to consist of a special tissue, Leonardo came to the conclusion that the heart was a muscle, saying:

"The heart is a principal muscle in respect of force" (MS. G. 1), and he goes on to look for its nerve supply and examine its blood vessels as for any other muscle.

In illustrating the structure of the left and right ventricles he used an inflation technique to bring into relief the papillary muscles, trabeculæ carnæ and moderator band.

"Before you open the heart inflate the ventricles of the heart, beginning from the aorta, and then tie them up and consider its quantity. Then do similarly with the right ventricle and right auricle; and thus you will see the shape of that which was created to dilate and contract itself and to revolve the blood" (Quaderni d'Anatomia **4,** 13).

FIG. 2.—Diagrammatic sketches of the aortic valve, showing its triangular shape and the eddies of blood which effect closure of the cusps (Quaderni d'Anatomia **4,** 14).

The papillary muscles, particularly in the left ventricle, are repeatedly drawn. Leonardo considered that their contraction caused shortening and widening of the heart in diastole; at the same time the cordæ tendinæ drew down the valve cusps to permit the inflow of blood from the auricles.

In a well-known experiment in which he observed the peasants of Tuscany killing pigs by driving a borer or "spillo" into the heart, he noted the movement of the handle corresponding to systole and diastole of the pig's heart. Though he observed correctly from these movements that the heart shortens in systole he failed to follow up these observations and still continued to believe that the cardiac impulse was produced by narrowing and lengthening of the heart—as was the Galenic tradition.

In his studies of the valves of the heart, Leonardo devoted most attention to the tricuspid and aortic valves which are repeatedly drawn open and closed. His conception of the function of the heart valves was that "always the valves of the heart, on the shutting of the heart, give passage to a quantity of blood first before they shut from within outwards" (Quaderni d'Anatomia **2,** 4). In the case of both the tricuspid and mitral valves he considered that this shutting was "perfect".

Galenic physiology considered that the mitral valve, having only two cusps, was imperfect. Air was supposed to be sucked from the lungs along the arteria venalis (pulmonary veins) directly into the left ventricle on diastole. Leonardo, as a result of his dissections of the bronchi and pulmonary vessels, as well as the experiment of inflating the lungs with bellows without producing any such passage of air, concluded that no air entered the left ventricle. His descriptions of the movements of the mitral and aortic valves confirm that he appreciated that blood and blood alone was concerned in their movements.

In his study of the aortic valve he made the experimental approach of constructing a model by pouring wax into a bull's aorta. He makes a glass cast of the aorta and describes "the form of the glass, to see in the glass, what the blood does in the heart when it shuts the openings of the heart" (Quaderni d'Anatomia **2**, 6).

Approaching the subject of the currents of blood in the aorta, he used the analogy of water spouting out of a pipe. Noting that the orifice of the aorta was triangular he observed that there were three laterally deviating currents of blood which impinged on the walls of the aorta entering the hollows, or sinuses, later named after Valsalva, and that these streams of blood returned towards the centre making impact on the valve cusps from below and from the side, closing them together in a vertical plane (Fig. 2).

"The heart is a vessel made of thick muscle, vivified and nourished by artery and vein as are other muscles"—was the point of view from which he dissected the coronary arteries, which are clearly shown arising from the aorta (Fig. 3) and followed out in detail through all their main branches, accompanied by the veins.

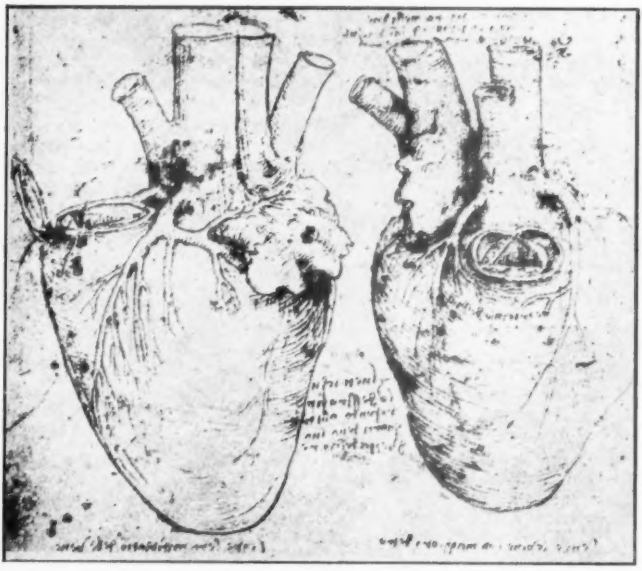

FIG. 3.—The origin of the coronary arteries and their course in relation to the pulmonary artery in a bullock's heart (Quaderni d'Anatomia **2**, 3).

The blood vessels of the body were dissected and illustrated by Leonardo in such a manner as to suggest that he followed Avicenna's Canon with conscientious accuracy.

During the course of his dissections, Leonardo came across the condition of arteriosclerosis and asks "why the vessels in the old acquire great length and those which used to be straight become bent, and the coat thickens so much as to close up and stop the movement of the blood, and from this arises the death of the old" (Dell' Anatomia Fogli B.10).

He suggests in answer to this question that the vessel wall swells as a result of absorbing increased nourishment from the blood.

Another pathological feature he noted was a hole in the atrial septum in the region of the foramen ovale. He writes "I have found from a, left ventricle, to b, right ventricle a perforated cavity from a to b, which I note here to see whether it is the same in the other auricles of other hearts" (Quaderni d'Anatomia **2**, 11).

Leonardo attempted to substitute the four powers of "force", "material movement", "weight" and "percussion" for the occult forces so freely invoked by Galen to account for the movement of the heart and blood. There is no doubt, however, that he accepted the Galenic pattern of movement of the blood towards the periphery where it was consumed by the organs and tissues. This movement was accomplished according to Leonardo by three

factors, heat being the most important, moving blood in the same way as fire carries smoke up a chimney, against gravity. The heart beat was of importance, and "natural gravity" played a role. Blood (cooled at the periphery) returned to the heart and superfluous blood, according to his idea, was excreted into the bowel, forming part of the fæces. He was thus a long way from the conception of the circulation as Harvey demonstrated it.

This failure has rather obscured the real advances that he made. As an illustrator of cardiac anatomy his drawings bear, with credit, comparison with any until recent years. He himself, judging from the amount of attention devoted to them, was most interested in his discovery of the auricles, or atria, as "upper ventricles" of the heart, and his investigation into the movements of the blood in eddies through the aortic valve.

For his achievements Leonardo surely merits a greater place in the history of cardiology than has up to the present been allowed him.

The illustrations are reproduced by gracious permission of H.M. the King.

The author hopes to produce a full account of Leonardo da Vinci's work on the heart in book form.

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[*January* 3, 1951]

The Lifework of William Harvey and Modern Medical Progress

By H. P. BAYON, M.D.

An essay to commemorate the tercentenary of the publication of *Exercitationes de Generatione Animalium*, London, 1651.

THE biography of William Harvey (1578–1657) has been so frequently examined in books and articles, and his opinions so often discussed in many orations that it might be assumed that no matter of any relevance has been overlooked. Still, it must be conceded that, beginning in his lifetime, an unfortunate controversy about the priority of the recognition of the circulation of the blood and similar non-essentials has been continued with great vigour, if not acrimony, whilst the cardinal significance of the methods he consistently practised and the doctrines he propounded have been misunderstood, if not ignored.

To-day, three centuries after his lifetime, we are in a position to appraise the influence of his writings, as a whole, on succeeding generations; more particularly we can decide whether his example inspired any researches or produced any results of medical significance. It will be of interest to try and ascertain how and to what extent Harvey succeeded in leading others to undertake those experimental researches to which we owe much of the contemporary scientific achievement and the triumphs of present-day biological medicine. It will not be denied that our diagnosis is more accurate, our therapy much more effective, our prognosis and prevention assured to a greater degree than they were in the days of Molière (1622–73).

It is intended to show that this progress is the direct outcome of the methods so successfully advocated and practised by William Harvey.

A few examples taken at random will illustrate the prevalent opinion shortly after the death of Harvey—and possibly even later—on the question of whether he played any part in furthering medical progress. Fontenelle (1657–1757) in his *Dialogue des Morts* (Paris, 1683) made Erasistratus say that whatever might be the real course of the blood-stream, mankind would continue to die. Or Sir John Floyer (1649–1734) who in the Preface to his book on the Pulse-watch stated: "Dr. Harvey gave the first credit if not the first rise of the opinion about the Circulation of the Blood, which was expected to bring in great and general innovations into the whole practice of physic, but it had no such effect" (London, 1707–10). Then William Hunter (1718–73) in *Two introductory lectures etc.* (1784), p. 47—in comparing the merits of Harvey with those of Christopher Columbus and Copernicus —wrote that the achievements of Harvey must rank comparatively low, because so much had been discovered by others, that little remained for Harvey but to dress it up into a system. These criticisms were related to the action of the heart and the circulation of the blood, but even more severe observations were those of Jan Swammerdam (1637–80) who in his *Historia insectorum generalis* (1699) asserted that Harvey, in studying the generation of animals, had, in his senile decrepitude, incoherently mixed truth and error, accuracy and falsity.

As a further example of misunderstanding is the often repeated misquotation of the dictum: *Omne vivum ex ovo*—which Harvey did not state with such lapidary brevity, though he explained the reasons for the opinion in several chapters of *De Generatione* (1651).

Many other quotations could be made, even from modern authors, to show that the name of Harvey is usually connected with the demonstration of the circulation of the blood and that the assumption is often made that this discovery, most interesting from the standpoint of physiology, did not influence the progress of medical practice. So that, apart from these or similar considerations, even understanding critics could say—in his century or the next—that the doctrines of Harvey were either sound or crackbrained, but could not prove that the methods he advocated and by which he supported his views, would gradually bear fruit and eventually lead to a far-reaching reform of medical practice. We alone can do this.

Still, every advantage usually carries with it some drawback; thus, whilst we gain by being able to learn how the doctrines of Harvey have stood the test of three centuries, we have lost in the meanwhile a full comprehension of the temper of his time and cannot say with confidence, how remarkable was the achievement of asserting and proving his opinions against those of Aristotle and Galen, which were universally believed, and had lasted unaltered for centuries—or how admirable and new were the means by which Harvey set about supporting and demonstrating his views.

In such a general consideration of the doctrines and methods of Harvey, taken as a whole, his investigations of the generation of animals have been usually relegated to the background and, if at all considered, have been presented with apologetic remarks to the effect that the mumblings of old age should be patiently tolerated, not accepted as the flashing pronouncements of brilliant youth. For example, two modern biographies of Harvey can be mentioned: that of Robert Willis (London, 1878) and that of D'Arcy Power (London, 1897). Both are outstanding and the latter author was able to quote many interesting details from the Minute books of St. Bartholomew's Hospital, to which he obtained access; but even he, when discussing in Chapter IX "The Treatise on Development", did not subject the book to the critical examination it deserves.

Now it is intended to commemorate the appearance of *De Generatione* (1651), not so much for its contents, as for the incentive it provided in furthering biological and medical progress. In approaching this task, a brief review of the previous writings of Harvey cannot be avoided, because it must be ascertained whether he successfully practised the methods he propounded and how much he owed to his predecessors and teachers.

By a singularly lucky chance, it is possible to follow the thought of Harvey throughout his working life, beginning with the notes for the Lumleian lectures, together with his printed works, and a certain number of his letters, which have been preserved, one of which was penned a few months before his death.

Taking first the *Prelectiones*, which would have been prepared some months before Harvey began his Lumleian lectures in April 1616, it is known how these notes—now safe in the British Museum—were mislaid, then recovered, to be reproduced in *facsimile* by the Royal College of Physicians in London, in 1883, accompanied by a printed deciphering by Edward Scott, M.A. It is said "deciphering", for the notes are not only in the execrable handwriting of Harvey, but consist of a mixture of bad Latin and colloquial English which only guesswork can interpret. Thus Edward Scott deserves all praise for having accomplished the task even if a few slips can be mentioned; e.g. the note on p. 75, attributed to "*Cæsalpinus Aretinus*". In my opinion it should read: "*J(ulius) Cæs(ar) Ar(antius)*"—which would be in keeping, for the remark relates to the action of the heart. Later, there is an observation (page 82): *ut ij qui carbonibus accensis Julian Imperator WH scoller of Cambridg*. The reference to the Cambridge scholar is easily understood; deaths by suffocation with carbon dioxide were not uncommon at the time, as the outcome of braziers in closed rooms. The reference to the Emperor Julian is not so easy; he died in his tent of wounds, though, possibly, some allusion was intended to his being choked by a gush of blood.

No less than ten pages of the MS. are devoted to the heart and its action, beginning with "*Cor a currendo quia semper movitur*" on page 73 and including the illuminating notes (page 78):

Autopsia { *vivo* / *mortuo* (N.B.—Autopsy = In the sense of: "Seeing with one's own eyes.")

ratione experimentum ligaturam.

It seems evident from the careful attention given to the action of the heart, that Harvey reasoned out his conception of the circulation as a result of the activity of the heart instead of the Galenical passive expansion, due to the *vis pulsifica* of the arteries and blood, by noticing the contracting hearts of snakes and fishes, which survive for some time.

On page 79 Harvey noted: "*Rationale etiam 1° Galeni experimentum de fistula impossibile.*" This refers to the well-known test of Galen with the quill in an artery (with which he proved

that arteries contained blood), which to succeed would require all the refined physiological experimental skill of to-day.

There has been a great deal of discussion as to whether Harvey was persuaded of the true facts of the circulation by mathematical, Aristotelian or any other method of reasoning. To me it seems obvious—notwithstanding the recorded conversation with Robert Boyle (1627–91)—that Harvey, having noted the heart in action outside and inside the body, gradually conceived the logical sequence, helped by knowledge of the function of the valves in the veins, which brought him to understand how the blood circulated continuously.

Among the contemporaries of Harvey, mention must be made of Nathaniel Highmore (1613–85), for his book on the *Anatomy of the Human Body*, published at the Hague in 1651, illustrates in the frontispiece, the circulation of the blood according to Harvey's conception, that is, without consideration of the existence of capillaries, uniting arteries and veins. Accordingly the drawing shows a pump pouring water, which soaking through the earth, no doubt, returns to the well. It is known that Harvey failed to notice the capillaries, the discovery of which was accomplished by Marcello Malpighi (1628–94) in 1661 in the lung of a frog. This missing link in the circulation was then confirmed in the tail of an eel by van Leeuwenhoek (1632–1723) and definitely clinched by the skilled injections of Fredrik Ruysch (1638–1731).

Before leaving the *Prelectiones*, it can be mentioned that it contains the note on page 73a: [*Cor*] "*fieri ex gutta sanguinis quae in ovo*" which shows—together with other remarks—that Harvey remembered his observations on hatching eggs made in Padua in his student days, with his teacher, Gerolamo Fabrizio (1533–1619); this also proves that the last book of Harvey was the fruit of prolonged thought.

Concluding—if the text of the *Prelectiones* has been neglected, it is because, being obviously difficult to interpret, it requires prolonged study and attention. All the same, it reproduces the inner working of the mind of Harvey in a manner not approached by any of his printed books.

Next we may consider briefly *De Motu Cordis et Sanguinis* (1628) which has received consummate attention over more than three centuries. It can be pointed out that the Preface, which says that the action of the heart and circulation of the blood had been demonstrated for more than nine years, seems to disagree with the lecture notes, which were dated April 1616. An examination of the course of the lectures reveals that the thorax and its organs would not be demonstrated till the third year; supposing the text of *De Motu* (1628) was written in 1627, this would make Harvey correct. Moreover Bayon (1939) showed that page 80 of the *Prelectiones*, which contains some of the reasons Harvey intended telling his audience, had made him accept the circulation of the blood, was written with a different quill from the one used for the remainder of the notes.

There has been some speculation why Harvey should have had his book printed and published in Frankfurt. The reasons seem to be twofold: one would be that his friend, Robert Fludd (1574–1637), recommended printing abroad, because foreign printers and publishers paid for texts and the other that William Fitzer (d. 1671) was an Englishman, as E. Weil (1944) has proved. This decision resulted in certain disadvantages: the Thirty Years' War (1618–48) and the crabbed writing of Harvey did not improve the text, which accordingly contains over 200 printers' errors, whilst the paper is of inferior quality.

As a specimen of the ignorant criticism with which *De Motu* (1628) was received can be quoted the remark of Emilio Parigiano (1567–1643)—a graduate of Padua—who wrote: in relation to the beats of the heart: "*Our poor deaf ears nor any physician in Venice can hear them; thrice fortunate those in London who can.*" In quoting this Daremberg (1870) said "*un témoignage honteux de la stupidité humaine*". Unfortunately Parigiano was not alone in his opposition, particularly in Italy, for he might have referred to Giovanni Nardi (d.1653?) as being on his side and also others. The great majority preferred quibbling vacuously to repeating the tests of Harvey; a notable exception was Daniel de Caux of Dieppe who in: *Varia philosophica et medica* (1674) published a confirmation of the circulation by means of experiments on cats.

A few words will suffice for the second book of Harvey—this consisted of two letters addressed to the French Anatomist, Jean Riolan, jr. (1580–1657) and bear the title: *Exercitatio Prima de Circulatione Sanguinis* and then *Exercitatio Altera*. Since the book of Riolan, the *Encheiridion*, was published in Paris in 1648 and the reply of Harvey was printed in Cambridge in 1649 (the year of the execution of Charles I—which affected his physician greatly) it is evident that there must have been some hurried composition and writing. It is therefore understandable that the tone is mainly polemical and some mistaken assertions are made, for example, that any difference in colour between arterial and venous blood was due to its having been squeezed through small apertures or that capillaries do not exist in the liver. This shows that Harvey had not grasped the significance of the oxygenation of the blood by the lungs, a problem whose solution had been attempted before his time, and was accomplished—if not in its entirety—within little more than a century after the

death of Harvey by Richard Lower (1631–91) and also John Mayow (1641–79). But for our present purpose, it is far preferable to restrict consideration to the definite achievements in ascertaining the active action of the heart and the continuous circulation of the whole blood. In relation to the heat of the body and the "spirits" in the blood, it must be admitted that Harvey was not in advance of the school knowledge of his time.

Next there is the third book of Harvey—the *Exercitationes de Generatione Animalium* (1651)—the MS. of which was entrusted by him to Dr. George Ent (1604–80)—an accomplished classical scholar—who edited it and supervised the printing. In the opinion of Herringham (1932) page 353—Ent corrected the text and greatly improved the style—a suggestion with which I agree.

Slight and slighting reference has been made to this text, because Harvey, misled by incomplete observations on the oviduct of a hen and those on an unsuitable object—*Cervidæ*—or the hinds and does of Windsor Park, decided that contact sufficed for the impregnation of a female. This erroneous conclusion would (or shall we say "could"?) have been avoided if Harvey had only seen the active spermatozoon in the seed of the cock-bird. In man, this essential element was discovered in 1677 by van Leeuwenhoek (1632–1723) and was then found to occur in the males of all vertebrates. What confused many observers was the wastefulness of producing myriads and myriads of "animalcules" to achieve the impregnation of a single ovum. During the whole of the eighteenth century the strife between "ovists" and "animalculists" continued, with arguments, some valid and some fantastic. Those who feel inclined to criticize Harvey for his wrong theorizing may be reminded that A. W. Meyer (1936) said on page 71: "*Even von Baer, who discovered the mammalian ovum had Harveian ideas regarding fertilization, for he thought that semen merely exerted an influence upon the ovum which, being somewhat inert, had first to be endowed with life by the sperm.*" More could be quoted from other authors, who had seen spermatozoa, to support the excuse that Harvey erred in good company.

It has been said that *Cervidæ* were an unfortunate choice for experimental embryogeny; this is because Meyer (1936), by referring to Bischoff (1936), made clear one of the reasons which induced Harvey to obtain erroneous conclusions. Bischoff (1936) showed that the Roe-deer, *Cervus capreolus*, has a considerable lag of time between fertilization and the naked-eye appearance of the product of conception. A similar delay in sheep misled Albrecht von Haller (1708–77).

To my mind the worst mistake of Harvey was not that he decided that fertilization took place without corpuscular contact, in a manner similar to a magnet acting on iron, but rather that he insisted that the child was born by its own efforts; a mistake he tried to support by many quibbles and petty conceits, whilst his experience at confinements should have convinced him of the contrary. That the muscular efforts of the mother give birth to the inert child had been observed by numerous previous Authors—but Harvey ignored their findings, preferring to defend his preconceived opinion by quotation from books, such as that of Gregor Nymann (1594–1638) or inconclusive observations, e.g. the infibulated pony mare of the Queen or the pregnancy in the prolapsed womb of a washerwoman. Having conceded the worst, it can be added that the advice given in the chapters *De Partu* is sound and practical, so that Herbert Ritchie Spencer (1927) could praise Harvey as having written the first original work on midwifery by an English author.

Whatever may be the faults of the text of *De Generatione* (1651) the Preface is a model of clear statement how to conduct researches in biological subjects—it is conclusive declaration of the right means for obtaining correct results in biological investigations. This Preface alone would place Harvey in the front rank as a founder of biological medical knowledge. The evidence for this assertion is easily provided, even if it is rare, perhaps even unique, that the work of a single man has such far-reaching consequences, no less than institution of a complete system of medicine, which, by its effectiveness has become universal, instead of being split up into several competing schools of thought and practice.

This development can be seen to be as straight as a ray of light. Harvey taught in various chapters of his last book that all living things came from an egg, even if he was wrong in his conception of what a mammalian ovum was. Then, the Italian Court physician, poet and academician, Francesco Redi (1625–98), quoting and inspired by Harvey, performed those clever experiments which proved that rotting meat could not produce maggots—a widely held view at the time—but that instead they developed from the eggs of flies. Next the English Jesuit, John Turberville Needham (1713–81) and the great Frenchman, Buffon (1707–88), performed their experiments showing that sterile broth in corked vessels in a few days would swarm with infusoria and bacteria. Thereupon Lazzaro Spallanzani (1729–99) repeated these tests and proved that prolonged boiling, together with secure closing, was required to obtain lasting sterility. From these tests and experiments the whole of modern bacteriology took its inception, with the most far-reaching practical applications. It cannot be denied or even doubted that all these investigations could have been brought to a successful conclusion without a full acce tance

and practice of the Harveian method of investigation. This consists in the combination of demonstrative experiment, together with comparative anatomical observations and bedside or clinical notes. All these means were practised by Harvey over a period of years. To consider him a pupil of René Descartes (1596–1650) or his imitator, because Harvey on one occasion calculated by arithmetic the output of the heart, is a statement lacking sufficient evidence.

A few words may be spared to consider the various names that have been mentioned as having antedated Harvey in the practice of experimentation for the solution of biological problems. This is all the more relevant for it has been said that Harvey was not the first to employ experiment for the ascertaining of facts. Here, instead it is stated that not only was he the first to publish the results of consequent experimentation for the solution of biological problems, but that he did so notwithstanding prolonged neglect and active opposition by his contemporaries. He thus lit a torch which cleared the path for others. It is therefore not irrelevant to the main purpose of this communication, to ascertain whether Harvey was the first in the field with consequent, comparative experimentation in relation to biological subjects, even if this involves delving into the past.

Little need be said of the philosophers of ancient Hellas, for they were too obsessed with the superiority of reasoning when compared with mere observation, to achieve much in experimental science. Even Aristotle was not without bias against experimental proof, for he was aware that the interpretation of single observations was what mattered, not the performance of tests. There were the numerous trials with poisons linked with the name of Mithridates, King of Pontus (111–63 B.C.), which were continued during centuries—but these were too restricted in scope for suitable comparison with later biological experiments. Galen of Pergamos (*c.* A.D. 130–*c.* 200) did perform several biological experiments and in some instances even obtained correct conclusions—but during centuries produced no imitators whose results are recorded. It can be mentioned that Farrington in two Pelican books has reviewed *Greek Science* with thorough scholarship and concluded that some Hellenic philosophers practised the experimental method for the purpose of ascertaining the presence of air—as distinct from mist—but even so their record is most rudimentary and scattered. The subject will be more fully discussed in the *Bulletin of the British Society for the History of Science*.

In the Middle Ages, when Scholasticism prevailed, rare, single biological tests were mentioned by Albertus Magnus (1193–1280) and also others, particularly Nicolaus Cusanus (1401–64), but the aim was restricted, the possibilities faintly perceived, the record unclear—because of the limitations of written, not printed, descriptions. Even the word "*experimentum*" differed from modern usage; it meant something actually seen or experienced. Such would be the trial whether an ostrich could really digest iron; or the suggestion of Cusanus to weigh a tree and earth before and after growth—an experiment actually performed by Johann Baptista van Helmont (1540–1616). It is true that Roger Bacon (*c.* 1214–98) wrote that the observations on the properties of the magnet by Peter Peregrinus entitled him to be a *magister experimentorum* and that Bacon mentioned *scientia experimentalis*. Still, none of those inchoate attempts, valuable as they may be as pioneer efforts, can compare with the complete experimental investigations of William Gilbert of Colchester (d. 1603), printed and published in *De Magnete* (*London*, 1600).

Harvey was acquainted with the work of Gilbert, whose book may well have served as a model for the researches of the younger physician.

The intellectual relations between Harvey and his patient, Francis Bacon (1561–1626), are not easily ascertained, for they seem not to have recognized each other's worth. Bacon wrote against Aristotelians—and Harvey was a great admirer of the Stagirite. Some of the remarks appear to be aimed at Harvey, who in his turn spoke slightingly of the Great Chancellor—if John Aubrey (1626–97) is to be believed. What seems evident is that both Harvey and Bacon held similar views in relation to experimentation and expressed them in resemblant terms—but Harvey practised what he preached !

René Descartes (1596–1650) and Bacon are frequently mentioned in relation to the inception of experimental science; but it should be mentioned that their aims in experimenting were totally different. Bacon wished to wrench forth the secrets of Nature by trials, test and critical experiments. Instead Descartes, having solved a problem by mathematical reasoning, would perform an experiment to place a coping stone on the edifice. The conception was quite separate and distinct.

Again, Galileo Galilei (1564–1642) stated clearly in his *Dialoghi* that he did not care if experiments showed anything differing from what had been mathematically reasoned and proved, for example the rate of falling bodies. He was justified in this belief, in having actually seen wood fall faster than metal, in any case at the commencement of the fall.

There remains to be mentioned Santorio Santorio (1561–1636); his aphorisms were what they claimed to be—pithy observations—which even if tested for their accuracy, need not

lead to further conclusions. They required the aid of chemical analysis to become the basis of metabolism.

One name can be added to the list, though not previously mentioned in this connexion—that of Realdo Colombo (d. 1559), assistant of Vesalius in Padua, later Professor of Anatomy in Pisa. It is true that Colombo was an expansive braggart and a proved plagiarist; but it is also undeniable that in his *De Re Anatomica* (1559) he stated the passage of the blood across the lungs in clear terms, supporting his opinion by anatomical, clinical and experimental observations. It may be said that in the early days after the publication of *De Motu Cordis* (1628) many thought that Harvey was merely reviving the ideas of Colombo. Instead the demonstration of the circulation of the whole blood stream, together with the action of the heart, was a complete doctrine. Incidentally, it can be learnt from the book of Juan Valverde de Hamusco: *De La Composicion Del Cuerpo Humano* (Rome, 1556), that Colombo was demonstrating the lung-passage in Pisa about 1545, that is several years before the printing of the book by Miguel Serveto in 1553.

Whether Vesalius knew of the lung-transit of the blood and did not dare to assert it freely, because it contradicted Galen too openly, must remain an unsolved problem.

It can be granted that there have been notable advances in medical knowledge and practice before and after Harvey, in which his method played little or no part. Such would be the use of mercury in syphilis, quinine in malaria, digitalis in heart-disease, vaccination, the recognition of the origin of puerperal fever—but even in this instance, the opinion of Semmelweis was supported by the experiments of Pasteur. None the less, the most rapid progress in all branches of medical theory and practice has been obtained by what I venture to call the Harveian method. Accordingly, it can be suggested that the link between the lifework of William Harvey and contemporary medical progress is provided not so much by the demonstration of the active action of the heart and the circulation of the whole blood, as by the practical actuation of the principles so clearly stated in the Preface of *De Generatione* 1651. In case this assertion should be understood as a contribution to the age-long dispute as to the respective merits of theory and practice, it can be made clear that Harvey made use of any means at his disposal for the attainment of Truth. It is obvious that unless he reasoned about his observations and made them agree he could not prepare his demonstrations or write his books. If any criticism is to be allowed, it is to the effect that far too often he indulged in speculation or ingenious conjecture, without the guide and control of relevant observations, whether clinical or experimental. For example, in his major error—considering that in mammals the fœtus was born by its own efforts; this was an application to human physiology of the action of the hatching chick in the egg-shell.

In relation to Biology in general, Joseph Needham (1934), in appraising the influence of Harvey on embryology, lists three critical remarks, the first of which is (page 128):

> "He did not break with Aristotelianism, as a few of his predecessors had already done, but on the contrary, lent his authority to a moribund outlook which involved the laborious treatment of unprofitable questions."

To my way of thinking, this is not an unfavourable judgment, because Harvey was not a rebel with a firebrand and axe in his hands (*colla fiaccola in man' e colla scure—Stecchetti*), but rather a constructive reformer, of which there are too few for the comfort of mankind. Moreover—in the words of Needham (1934)—Harvey handled the question of growth and differentiation better than any before, anticipating the ideas of the present century.

As a medical practitioner Harvey could not be and was not in advance of his century, except that he took an interest in midwifery and was in favour of non-interference with natural processes—a modern standpoint. He also seems to have undertaken surgical operations.

Even if Harvey prescribed "*Pulvis ex ebore et calcaneo cervi*" (Ivory powder and that made from the heel of a stag) and that developments from the application of his methods took nearly three centuries in coming to fruition, yet the present-day triumphs in preventive medicine, the use of powerful specifics and effective antibiotics, are the direct outcome of the Harveian method of solving biological and medical problems.

It is for this reason that we are gathered to-day to recall the lifework of a man, who, if not great, achieved great deeds and propounded lasting doctrines.

The lecture was illustrated by lantern slides kindly lent by the Wellcome Institution (Dr. E. A. Underwood).

Section of Anæsthetics

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Fires and Explosions Connected with Anæsthesia. [*Abridged*]

PRESIDENT'S ADDRESS

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I HAVE chosen this subject for my Presidential Address for several reasons. Firstly, because many fires and explosions which have occurred could have been avoided. The American Society of Anesthesiologists made the following assertion in their report: "Our present-day knowledge of the ætiology and prophylaxis of all anæsthetic fires and explosions is sufficient to prevent all further anæsthetic combustions." And yet they do continue to occur! Secondly—under the National Health Service—construction and re-equipment of operating theatres is occurring throughout the country and anæsthetists' views will be taken into consideration. They must know what is required to safeguard the patient and theatre staff from this type of accident. Thirdly, the surgeon of to-day uses the diathermy, cautery, X-ray and a multitude of "scopes" for peering into the interior of the human body, much more frequently than in the past. And lastly—and I feel that this is the most important reason—I want to refresh your memory that it is nearly always the patient who suffers most and in some cases, I regret to say, actually loses his or her life. Nothing can be more tragic. Luckily in this country this accident is not common.

I wrote to an anæsthetist at each of the teaching centres in England, Scotland and Wales and all very kindly sent me what information they could find in regard to this matter. Most, I am glad to say, were unable to supply any information. From one centre regret was expressed that they had to report that they had had no fires or explosions. This they attributed to maintaining a very high standard of precaution. My correspondent wrote: "We do not believe that any potentially dangerous equipment should be used within an hour of the administration of an inflammable anæsthetic to a patient." From another source, I learnt that since 1930, 170,000 anæsthetics had been given in a certain Infirmary and only one explosion and fire had occurred.

I intend to illustrate various points by extracts from the accounts of accidents which have happened.

One of the first reports of an anæsthetic explosion in this country appeared in the *British Medical Journal* of 1892 (ii, 1457). In America as early as 1896 they decided to try to minimize the fires and explosions which frequently occurred, and organized the National Fire Protection Association, a body which has just published an up-to-date code of practice.

In February 1938 in this country the Institution of Electrical Engineers and the medical profession formed a committee called the Operating Theatres Electrical Apparatus Committee. The medical side was as follows: the late Mr. Lionel Colledge, Dr. C. F. Hadfield, and Mr. Souttar—or Sir Henry, as he is now. This Committee began its investigations in February and March 1939 but before much progress had been made these were suspended due to the war. Dr. Hadfield in March 1943 drew attention to the regrettable prevalence of fatalities caused by anæsthetic explosions. As a result, the deliberations of the Committee were resumed. In March 1944 the Minister of Health decided to circulate the Warning Notice to all hospitals in this country and through the Armed Services to all Service hospitals abroad. It is a very comprehensive document and well worth reading. It should be found clearly displayed in or near all operating theatres.

Before a fire or explosion can take place, two conditions are necessary:

(1) The presence of an inflammable liquid or vapour in sufficient quantity.
(2) A source of heat sufficient to raise the liquid to its "flash point" or the vapour to its "ignition temperature".

Take the first condition. In anæsthesia the following drugs will ignite in liquid form and also give off an inflammable vapour: Ethyl chloride, ethyl and di-vinyl ethers. There has been some controversy in the medical press of late as regards the explosibility of ethyl chloride. There is no doubt that liquid ethyl chloride is inflammable and that when mixed with 5 to 15% of air it is explosive. It is rarely used with oxygen but a mixture of ethyl chloride and oxygen would explode with extreme violence. Ether is inflammable in liquid form, but—and here I quote from Hewer (1948)—if ether is contaminated with peroxides it will ignite in the liquid state at a temperature of 100° C., that is, at the boiling point of water. Ether vapour will ignite at 184° C. It is also well to remember that a mixture of nitrous oxide, oxygen and ether is more highly explosive than ether and oxygen. This is

due to the fact that nitrous oxide disintegrates at temperatures above 450° C. and therefore the initial temperature of the explosion will liberate more oxygen by disintegrating the nitrous oxide, thereby stepping up the violence of the explosion. I shall here quote two cases showing the difference between the risk of using ether and air and ether and oxygen.

(1) Endotracheal ether was being given by insufflation for some facial operation and an electric pump produced the stream of air. A cautery was used and this lit the escaping ether vapour which burnt above the patient's mouth like the flame of a blow lamp, until the flow was cut off! The patient was not burnt. Had oxygen been used, the mixture would have detonated in the patient's lungs.

(2) A patient for laryngoscopy was anæsthetized with ether—the anæsthetic being maintained by blowing ether and oxygen through a hook into the mouth. The surgeon seated at the head of the table turned on the laryngoscope light which was connected to a rheostat supplied by the mains. Having turned on the laryngoscope he talked to the students for a minute or so and then turned round to put this instrument into the patient's mouth. There was an immediate explosion—the surgeon was flung from his seat on to the floor and a flash travelled back, wrecking the Boyle's machine, scorching the anæsthetist's hands and face and singeing the front part of his head. The patient died immediately and a post-mortem examination revealed extensive damage throughout the whole of the bronchial tree, the lungs being ruptured and contused throughout—in fact, a picture of blast injury. On investigation with the help of the National Institute of Physical Research it was found that the light bulb of the laryngoscope fed from the rheostat reached a considerable temperature in a very short space of time and that with the temperature obtained when the lamp was turned on for sixty seconds, certain concentrations of ether and oxygen could be exploded.

Next there are the gases, used in anæsthesia, which will ignite and explode when in contact with a source of heat: Ethylene, acetylene (both of which are used but rarely if ever in this country) and, of course, cyclopropane. When pure, cyclopropane will burn in air. The following table gives the limits of explosibility in air, oxygen and nitrous oxide, as shown so admirably by Hewer (1948*a*). For comparison I have put the figures for ether vapour and air, and ether and oxygen above the cyclopropane figures.

Ether	In air (Inflammable)	3% to 9%	Ether
	(Explosive)	19% to 34%	Ether
	In oxygen (Explosive)	3% to 80%	Ether
Cyclopropane ..	In air (Explosive)	3% to 8·5%	Cyclopropane
	In oxygen (Explosive)	2·5% to 50%	Cyclopropane
	In nitrous oxide	3% to 28%	Cyclopropane

Nitrous oxide and oxygen mixture has been said to have caused an explosion, but I cannot help feeling that there must have been a trace of some other agent such as ether or cyclopropane residual in the apparatus in these cases. On the other hand, as I have already stated, there is no shadow of doubt that nitrous oxide mixed with ether and oxygen steps up the violence of the explosion.

Now to take the second condition—namely a source of heat sufficient to raise the liquid to its "flash point" and/or the vapour to its "ignition temperature". The "ignition temperature" will be raised by lowering the percentage of oxygen present and lowered by increasing the pressure of the vapour mixture. The converse is true in both of these conditions.

Because a heated body such as a cautery is not visible as red-heat, it is no guarantee of safety. If any of you cook on an electric stove you will no doubt have burnt your fingers on the hot plate, although it shows no sign of redness. For instance the temperature of the tip of a cautery when it is visibly red-hot is in the region of 400° C. and above. On the other hand ether and oxygen mixtures can be ignited at 184° C.

The sources of heat in connexion with anæsthesia are best divided into two groups—Electrical and Non-electrical.

Electrical.—There are two kinds of electricity: (1) Electric current, either D.C. or A.C., and (2) Static. Both produce sparks and the danger arises as soon as the spark is of sufficient strength to raise the temperature of the liquid to its flash point or the vapour to its ignition temperature.

(1) In the electric current there is the added danger of overloading the circuit and producing heat, either in the case of the lamp bulb, which can get sufficiently hot to explode the mixture or in the case of wiring, which is not capable of carrying the extra load. As an example, suppose you plug an electric stove into a lighting circuit, the wiring will not carry the current required by the stove and so becomes very hot. This is often the cause of fire in a house.

If the flow of current through a lamp filament is increased by raising the potential or voltage the filament becomes hotter and hotter to intense white heat and finally melts, or fuses as we say. I gave an example of this just now where the laryngoscope bulb was overheated. This explains the danger of using a rheostat with a supply of current from the mains. It is so easy to overload the lamp. A dry battery of the correct voltage, 6 or 4 volts whatever it is, is without risk.

If the wire carrying a current be broken a spark will occur, but the intensity of the spark is governed by the flow of current, the amperage. Take for example the switching on and

off of a pocket torch. There is a spark, but so minute that it cannot be seen and is usually harmless, but remove the cover from an ordinary domestic electric light switch and each time you switch it on and off quite a distinct spark will be seen. Here is an example where a pocket torch did ignite and even explode ether vapour: it occurred during a throat operation under general anæsthesia.

The anæsthetist was using a Shipway apparatus and Davis gag. Induction was by ether and oxygen and when the operation was about to start the ether was turned off and chloroform used. The ether bottle, however, had been surrounded by very hot water and as the surgeon used a pencil torch for some purpose an explosion occurred which flashed back to the ether bottle, which burst. The fire was quickly controlled. The surgeon sustained a cut eyebrow and apparently no other personnel was affected. However, the patient developed pneumonia and died a week later. At post-mortem pieces of glass were found embedded in the mouth and pharynx.

Thomas (1950*a*) calls these sparks "break" sparks. There is also another type of spark which he calls a "wipe" spark. The "wipe" spark is the spark seen when an electric motor is running and occurs between the brushes of the motor and its armature. Such sparks are met with in suction or other motor-driven apparatus. Break sparks of low voltage are of short duration—by this I mean a few thousandths of a second—too minute in fact to produce much heat. Break sparks of higher voltage than 100 volts tend to develop into an arc or continuous discharge of sparks, the best example of which is the high-frequency current used for coagulation. These are naturally liable to ignite and/or explode an inflammable vapour.

(2) Now a few words about "Static" electricity.

Static charges are set up wherever friction occurs. The quantities are usually very small even though the potential may be great. More often than not the charges arise on conductors and quickly leak away; it is only on good insulators where ion movement is very limited that the charges stay put and so become detectable. For this reason they are called "Static" charges and the force between them is often called electro-static force.

When two objects having different electric potentials are approaching contact, a spark will occur. Thomas (1950*a*) calls these sparks "jump" sparks. These differ from the "break" spark which occurs when the conducting medium is broken and the ends are parted. Static electricity can be discharged to earth.

Static sparks will not usually occur in air unless the voltage is above 350 volts or if they do occur they are less than 1/1000 of an inch in length and quite incapable of igniting an inflammable vapour. In general, static sparks are of short duration—about 1/1,000,000 of a second. Their discharge is usually oscillatory in character—the greatest amount of the charge passing in the first oscillation or perhaps in as short a time as 1: 100 millionth part of a second, but here is the danger—the flow of current in that infinitesimally short space of time may reach as high as 100 amperes when the voltage is high. This kind of current will of course result in the ignition and possibly the explosion of an inflammable vapour. Static electricity can be generated in the operating theatre in many ways, even by the passage of dry gases along the inside of the elephant tubing which connects the ordinary Boyle's machine with the patient. The amount is, however, very small. It may be increased by the presence of dust and reduced to a negligible quantity when the inside of the tube is rendered moist by being immersed in water before the anæsthetic is started. The rest of the causes are clearly displayed on the Warning Notices in or near all operating theatres. The type of atmosphere which favours the production of static charges is the cold dry variety with high barometric pressure. This is not often found in this country, but frequently occurs in America. In modern theatres with air-conditioning this should not be present, but it is important to remember that the humidity of the air plays its part.

Thomas (1950*b*) calls attention to the voltage—5,000 to 15,000 volts—obtained on an un-grounded theatre trolley when a sheet or blanket is withdrawn across the mattress or the mattress is rubbed a few times with a dry hand.

A correspondent sends me the following account: "Whilst anæsthetizing a neurosurgical case in 1933 I had occasion to stretch my hand out to the anæsthetic machine in order to cut down the rate of flow in the ether drip. There was a sudden large spark from my index finger to the machine before I made contact with the latter and this set fire to some ether which had been seeping through a fine crack in the apparatus. The apparatus was enveloped in flames which were quickly put out and actually little damage was done. The patient was unharmed. The explanation of the accident is simple. My feet were on a thick non-conducting rubber mat and when I was taking the pulse, often at the same time as the diathermy was being used, I became charged up like a condenser."

Under *Electrical* I must of course mention the cautery and diathermy. Need I say any more about these two *bêtes noires* of the anæsthetist's life?

Non-electrical.—In this group come fires of all sorts: coal-fires—gas-fires—cigarettes—matches—the dropping of heavy metal objects upon a stone or composition floor causing a spark—sterilizers such as portable ones with a methylated burner to heat them—even the hot air syringe used by dentists. All these and no doubt other sources such as candles and paraffin lamps are met with, usually in private houses and seldom in hospitals, except perhaps the cigarette and match.

And lastly, *spontaneous sources of heat.*

When the "Endurance" type of reducing valve was fitted to oxygen cylinders and when, during the war, the oxygen cylinders were filled 10% above pre-war pressures, fires occurred on several occasions. This was usually due to someone turning on the oxygen rapidly and fully. The valves were changed to the "Adams" type, since when the trouble has ceased.

Oil and grease should never be used in contact with highly compressed oxygen, nor should a reducing valve which has been used for nitrous oxide be switched over for use with oxygen, since a very fine film of oily substance is left behind in the valve by the N_2O.

The risks attached to each individual drug or gas.

Ethyl chloride.—As a liquid it is very inflammable and therefore should be treated as any other inflammable liquid. As a vapour in concentration of 5 to 15% in air it forms a highly explosive mixture. It should not therefore be used anywhere near a source of heat. In one of the letters I received in reply to my queries, the correspondent himself had had a wart removed from his abdominal wall with a diathermy needle after the surgeon had frozen the spot with ethyl chloride. The victim described his burns with feeling.

Ether.—Di-vinyl and ethyl ethers have vapour densities of 35 and 37 respectively. Di-vinyl ether is very unstable and decomposes rapidly when exposed to the air, but is explosive when mixed with air, oxygen or nitrous oxide. Ethyl ether is highly inflammable and volatilizes readily at ordinary room temperatures. The vapour—over two and a half times heavier than air—sinks rapidly to ground level and tends to spread out over the surface of the floor without mixing with the general atmosphere. Herein lies one of its dangers—that of ignition at ground level at some remote spot which initiates the "cool flame": this travels slowly and is invisible in daylight. The result may be an explosion close to the patient without any warning.

As an actual example of this: For a throat operation, ether was being insufflated through a Davis gag. The surgeon used a headlight connected to a battery on the floor behind his stool. During the operation the headlight went out and a fire started around the battery on the floor. This was due to worn leads producing a sufficient spark to ignite the ether vapour which had travelled along the floor. No injury was caused either to patient or personnel, and there was no explosion.

As I noted earlier in this paper, ether ignites in air between small limits of concentration; that is from 3 to 9%; it explodes between 19 and 34%. If ether has to be used in the presence of a source of heat the mixture should be made with air and not oxygen or nitrous oxide and oxygen. Remember that the addition of oxygen to ether vapour increases the limits of inflammability and explosibility to from 3 to 80%. Hewer (1948*b*) also points out that fatal accidents have occurred from the use of a diathermy needle on skin prepared for operation with ether or spirit. Contamination with peroxides lowers the ignition point of liquid ether and it may ignite at as low a temperature as 100° C. Contamination of ether by peroxides is very easily produced by strong sunlight. It is important therefore to see that ether bottles are not exposed to sunlight, that the bottles themselves are made of coloured glass, and that where wicks are used, these are removed, rinsed and dried daily. Some copper should be immersed in the ether to act as an anticatalyst: all Boyle's ether bottles have the "U" tube and plunger made of copper.

Cyclopropane has a vapour density of 21·025 and is therefore heavier than air and tends to sink to ground level, but it is seldom used in this country except in a closed circuit and if a leak occurs the vapour readily diffuses into the atmosphere and becomes too weak to ignite or explode. On the other hand if the source of heat such as a diathermy or cautery approaches too close to the leak, an explosion will occur. Most workers have claimed that the danger area is within a foot of the leak. Greene (1941*a*) collected 10 cases in which ether, ethylene and cyclopropane have been ignited more than 12 inches from the nearest leak, but could find no fatality caused by the presence of cautery or flame outside a 12-inch radius surrounding the upper respiratory tract.

The following description of an explosion using cyclopropane and oxygen brings to light several interesting points. The operation proposed was a subtotal gastrectomy for a chronic duodenal ulcer. The patient was 64 years of age and fairly fit. A cuffed orotracheal tube, size No. 10, was passed and was connected up to the Coxeter-Mushin absorber using Nosworthy's attachments. The cuff was inflated and the circuit checked up to ensure it was airtight. The oxygen was run at 200–300 c.c. per minute, and the cyclopropane at 50–100 c.c. per minute. With this rate of flow the bag generally filled and had to be emptied several times during the operation.

My correspondent goes on: "After the operation had progressed for about an hour, the duodenum had been mobilized, clamped and sectioned. At this time the patient was under controlled respiration but as the effect of the curare was beginning to wear off, I got up and moved round to give a further dose of curare from the syringe strapped to his right arm.

"I went back to my seat and leaned forward towards the machine to pick up the bag and tubing which had been put down on the lower shelf of the Boyle's machine. As I had the tubing in my hand there was a sudden explosion which deafened everyone, and I saw a 'ball of flame' at the site of the rebreathing bag. For a moment I couldn't think what had happened, and then hurriedly looked at the patient. He was very pale and his pulse volume poor, rate 60 per minute. As he had been on controlled respiration and he was not breathing I immediately sent for another machine and connected

up. He began breathing spontaneously soon afterwards, and his general condition improved very considerably. The operation was continued, as it had reached such a stage that it could not be terminated, and there was no indication to me at that time that the patient had suffered any great harm.

"Fifteen minutes later his pulse volume became weaker although his pulse remained steady and he became rather cyanosed, and soon after this his respiration became 'bubbly'. I aspirated his lungs and obtained bright red blood and clots. So I then put up a blood drip.

"The operation was proceeded with as quickly as possible. I kept aspirating blood from his lungs. The pulse remained steady at 88, and was a good volume.

"At the end of the operation the patient was kept in theatre and watched. He was breathing well, his colour was good and his pulse-rate and volume were both satisfactory.

"He then began to develop emphysema, first of the cervical region and then of the thorax, and his colour became poor.

"A bronchoscope was passed and several blood clots were removed. There was damage and emphysema of the tracheal mucous membrane. Portable X-ray showed no pulmonary collapse and no pneumothorax. His condition slowly deteriorated and he died five hours later.

"The only damage to any member of the surgical team, &c., was to myself. I received one or two small lacerations on the back of the left hand.

"The machine used was the standard Boyle's with a Coxeter-Mushin absorber. The concertina type rebreathing bag had been modified by being replaced by a length of corrugated tubing with a Magill rebreathing bag at the end. Prior to the explosion there was no evidence of a leak.

"The explosion caused both glass domes to be cracked, the Magill bag and tubing was burst and the connexions to the machine and the Nosworthy's connexion were blown apart.

"Throughout the whole operation no diathermy or electric apparatus was used. The sucker was a hydrostatic one. There was one spotlight standing about 1–2 feet from the machine. This was checked afterwards and found to be in perfect order.

"The Home Office sent someone to investigate. The only thing which he told me was that the conductivity of the floor was not up to standard. It is one of those composite floors with small marble chips intersected by brass strips."

Precautions to prevent fire or explosion during anæsthesia.

The obvious answer to this is never to use any drug or gas which is inflammable as a liquid and explosive as a gas. This would of course be absurd until such time as research workers produce either the perfect anæsthetic drug or the perfect anæsthetic gas. On the other hand, I cannot help feeling that the advent of muscle relaxants has gone a very long way in helping to reduce the fire and explosion risk. When dealing with the anæsthetic for any operation which involves the respiratory tract, it is quite possible to produce and maintain a light plane of anæsthesia by using a muscle relaxant followed by nitrous oxide, oxygen and trilene or very small and repeated doses of thiopentone in place of the trilene. It is, however, of the utmost importance that the anæsthetist using this method should be thoroughly conversant with the right technique, by which I mean pre-operative treatment, the anæsthesia itself and post-operative treatment, especially during the time between the end of the operation and the patient's return to the ward. I have taken the respiratory tract first as I feel that the risk of explosion and its resultant fatality is most likely to occur in this particular province. Further down the body—abdominal work for instance, where the surgeon wishes to use a diathermy or a light inside the abdominal cavity—the risk of explosion if ether or cyclopropane are used in a closed circuit is considerably reduced, provided that it is remembered that the foot switch on the floor should be of the spark proof type, and that diathermy and suction apparatus must be placed three feet above floor level as a minimum. On the other hand there is choice between two methods for abdominal work combined with "sparks": analgesic drugs can be used as regionals, field blocks or spinals, or the muscle relaxants used with a light plane of anæsthesia as described above. One of my correspondents performed an interesting experiment to prove to the surgeon that the stomach contains an explosive mixture, when ether and oxygen are used, and that a diathermy is dangerous in these circumstances.

"The outer end of a stomach tube was led into an open bucket placed by the operating table during a gas/oxygen/ether anæsthesia for a gastric operation. At the end of the operation, the bucket was taken outside the theatre and a lighted match thrown in—the resulting explosion quite convinced the doubting surgeon still within the theatre!"

Another correspondent writes: "A diathermy needle was used to open both gall-bladder and stomach. Gall-bladder opened normally; on diathermy needle entering stomach there was a very violent explosion. Anæsthetic apparatus in use at this time was a Boyle's gas and oxygen machine delivering a mixture of gas, oxygen and ether. As the mask was a very good fit for the patient's face, held in place with a Clausen's harness, and the diathermy was some distance away, no great danger had been anticipated. I myself, after being momentarily stunned by the explosion, found myself with multiple superficial lacerations of the face, a perforation of the right ear drum, and my theatre gown on fire. This resulted in some slight burns to my right arm. The theatre windows were open as it was a very warm day and were undamaged, but a glass instrument cabinet against the wall was broken. The surgeon had a traumatic perforation of the left ear drum, the assistant surgeon and the house surgeon a perforation of the right ear drum. Theatre personnel were otherwise unhurt. The patient did not appear to be much the worse and the operation was finished. The patient recovered from operation but died some six weeks later from the carcinoma of head of pancreas."

During abdominal operations as in all other operations when a sucker is used, it is most

important to see that it does not spark, or if it does that it is placed at such a height that it is above "leak level", except in the case of ethylene, which has a vapour density lighter than air and therefore floats.

The ideal operating theatre and anæsthetic room.—Ignition and explosion risks can be very considerably reduced if:

(1) The floor is conductive and grounded. It is no good attaching chains to apparatus hoping to earth them if the floor is covered with non-conducting rubber. Composite floors can now be laid which comply with the above requirements. In country districts where the floor in the cottage hospital may be of linoleum or other insulating substance, much can be done by swabbing the floor with water prior to anæsthetizing patients.

(2) Humidity. This is a very vexed question. Greene (1941*b*) in his analysis of cases of explosion during anæsthesia found that only 2 cases occurred when the humidity was 60%; 3 cases when it was around 55%; and 32 when it was below 50%.

(3) All apparatus must be earthed to the floor and the proper way to do this is to have chains—two chains to each piece of apparatus in case one comes adrift—and to see that these are chains of non-spark-producing material, such as brass, and that they are of sufficient length to trail on the floor. If rubber cups are used on the feet of stools, surgeons' platforms, &c., they should be of conductive rubber. Trolleys and operating tables should be earthed. There should be conductive rubber tyres on trolleys and the mattresses should also be of conductive rubber. Before the anæsthetic is started the blankets should be replaced by towelling.

(4) Personnel should be shod in conductive rubber boots or if they wear leather this should be damped with water and kept moist during the danger period. Clothing should be of cotton—I mean the outer clothing—as silk, rayon and wool are good media for generating static electricity.

(5) Light and power switches should all be at a level not less than three feet from the ground, and in the case of power switches and all switches carrying a heavy current it is much safer to have a non-spark mercury switch. This is done by placing mercury in a sealed tube so that in one position it makes contact and in another position contact is broken. Any sparking occurring will be sealed off inside the tube. If electric stoves are used to warm the theatre they may safely be used provided they are placed not lower than seven feet from the floor level. All suction machines should be outside the theatre and "ports" only to which the sucker can be connected inside the theatre.

In most private houses or flats there is an electric or gas fire, and these can be very easily turned out before commencing the anæsthetic, but in the old days and in the country to-day it is not uncommon to find a really nice coal fire. There is one famous nursing home in London at the present time that still allows patients the luxury of a coal fire in their bedroom. Here is a method of dealing effectively with this hazard in a rapid and clean manner. Take a couple of sheets of cotton-wool the full width of a pound packet and about a foot wide. Dip them in water and by gently squeezing remove sufficient water to prevent them dripping on the carpet. Lay them over the fire just as it is and they should be big enough to cover it completely from the back right over the front bars almost to the floor level. If it is a very big fire another wide strip can be placed on the top of these, but it is seldom necessary. By the end of the operation they will be almost dry and can easily be removed as the fire, although still sufficiently good not to require relighting, is well under control.

(6) Smoking and the throwing down of matches have already been mentioned.

When a fire or explosion does occur, I should imagine that it is difficult to collect one's senses and do something quickly, but I am quite sure that this time-lag will be greatly reduced if one has a clear idea of exactly what line to take, should this tragedy occur. The first essential is to free the patient from all contact with the machine, and this should be done automatically by the anæsthetist in the shortest possible space of time. Should an oxygen cylinder catch fire at the valve it will flame with intense heat: if it happens as the cylinder is turned on, turn it off quickly—you will get no second chance to do this. If it is too late to turn it off because of the heat, try to remove as many as possible of the inflammable objects from its immediate vicinity and to stand by with a fire-extinguisher to deal with any object fired. It may take a little time but it will eventually burn itself out. In case of fire it is important to know exactly where the fire-fighting apparatus is—and it should be placed in a spot easily accessible from either theatre or anæsthetic room. For an ether or spirit fire the foam gun is the best, but care must be taken not to use it too close to the liquid or this will be blown out over a larger surface.

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Section of Pædiatrics

President—KENNETH H. TALLERMAN, M.C., M.A., M.D., F.R.C.P.

[*October* 27, 1950]

Microcephaly with Chorioretinopathy, Cerebral Calcification and Internal Hydrocephalus.—ANDREW BOGDAN, M.D. (for N. O. RICHARDS, M.D.).

Marilyn P. was first seen in May 1950, at 5 months of age, because of feeding difficulty and failure to gain weight. Microcephaly and mental retardation were first noticed at this time and the child admitted for further investigation.

Personal history.—Second of two children. Birth-weight 6 lb. 2 oz. One week premature. Normal delivery. Jaundice three hours after birth, lasting a week. No fits or hæmorrhagic manifestations.

Family history.—Sister well and normal. Father and mother well; the latter has had nothing to suggest clinical toxoplasmosis, though suffers from asthma. Paternal uncle suffers from amentia.

Examination (May 1950).—Head circumference 14 in. Anterior fontanelle closed. Sight impaired. Pupils normal, react to light. Variable strabismus. The only milestone achieved then was some control of head movements. Fundi (examined by Mr. P. D. Trevor-Roper) both discs oval and pale. Right-sided generalized retinal atrophy, macula normal, some peripheral granular pigmentation. Left side shows a localized macular patch of chorioretinopathy, and peripheral granular pigmentation (Fig. 1). Spasticity of upper and lower limbs. Reflexes brisk. Plantars extensor. Heart, lungs, abdomen, urine all normal.

FIG. 1.—The left fundus with optic atrophy, a large area of chorioretinopathy at the macula, and peripheral granular pigmentation.

Investigations.—X-rays (Dr. L. J. Rae). Skull: Area of calcification in the left parietal area. Pneumo-encephalogram: marked atrophy of right cerebral hemisphere. Bilateral internal hydrocephalus, especially of the left side. The calcification is related to the left lateral ventricle (Fig. 2).

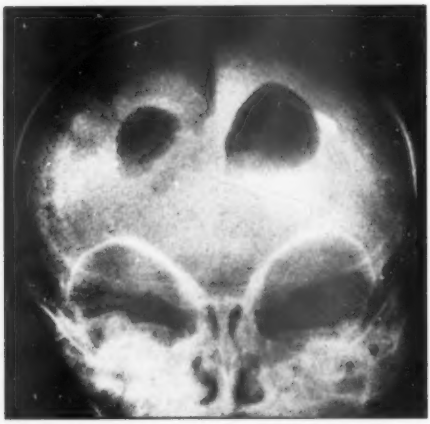

FIG. 2.—Pneumo-encephalogram, showing cerebral calcification, internal hydrocephalus and cortical atrophy.

Cerebrospinal fluid clear and colourless. Cells less than 3 per c.mm. Sugar 65 mg.%. Pandy's test negative. Proteins 20 mg.%. Chlorides 700 mg.%. Lange curve 000000.

Blood: Hb 80%; W.B.C. 13,400. Normal differential count. W.R. and Kahn reactions negative. Both mother and patient Rhesus positive.

Toxoplasmosis investigations:

	Mrs. P. (the mother)	A (the sister)	B (the patient)
Intradermal 1/500 toxoplasmin test	Positive	Negative	Negative
Cytoplasm modifying antibody test (Sabin)	Positive (titre 1 : 32)	Negative	Negative
Complement-fixation test	Positive (titre 1 : 16)	Negative	Doubtful (1 : 2)

These tests were also negative on the C.S.F.

Examination (October 1950, aged 10 months).—Gaining weight, though still difficult over feeds. Smiles, and now gives an impression of some emotional development. Sight appears to be improving and the chorioretinopathy at the left macular site appears "harder". Head control has improved, though still does not sit up. Head circumference now 15¼ in. Spasticity of limbs more marked.

Comment.—This case appears to be one of the first of its kind described in this country. Chorioretinopathy associated with other evidence of cerebral damage in childhood has been described as a syndrome of unknown ætiology and separable from congenital toxoplasmosis (Sabin and Feldman, 1949). The cytoplasm modifying antibody tests and complement-fixation tests were negative in all the children of their series, and the maternal titres were also negative, or of insignificant level, unlike the maternal titres in this case. These Sabin (1950) feels can have no bearing on the ætiology of the patient's condition, in view of the child's negative titre.

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Punctate Epiphyseal Dysplasia.—HUGH JOLLY, M.R.C.P. (for REGINALD LIGHTWOOD, M.D.).

Susan P., aged 10 weeks.

History.—Only child of healthy unrelated young parents. Born 10.8.50 by Cæsarean section three weeks before term, following failed version of a breech presentation. Birth-weight 5 lb. 10 oz. At birth baby was well but right arm and leg were short and there was scaliness of the skin particularly on the right side.

On examination.—Slight asymmetry of skull. Right torticollis. Limbs: Both right arm and right leg held flexed and are very short, due mainly to small length of humerus and femur (Fig. 1). The right middle finger is short. Skin appears normal but some stiffness of right arm and leg. Equinus deformity of right foot. Eyes (Mr. J. H. Doggart): Faint diffuse haziness of both corneæ. Right lens shows peripheral striæ of opacity, an unusual form of partial cataract. Left lens clear. Bilateral optic atrophy.

FIG. 1.

FIG. 2.

FIG. 1.—Photograph of child showing short right arm and right leg.

FIG. 2.—Radiograph of right foot, showing typical changes of the disease.

Investigations.—Serum alkaline phosphatase 29 units. Blood inorganic phosphorus 6·0 mg.%. Serum calcium 11·2 mg.%.

X-rays show the typical changes of punctate epiphyseal dysplasia in which the epiphysis appears to be ossifying from a number of separate centres, so producing a stippling effect. This is most marked in the right arm and leg, particularly humerus, femur, carpus and tarsus (Fig. 2), but is also present to a much less degree on the left side. Vertebral column and rib ends also involved.

The X-rays were originally seen by Dr. A. Elkeles, who made the diagnosis.

Comment.—This disease was described for the first time by Fairbank in 1927 and named by him in 1935; one case, however, had been previously recorded by Conradi in 1914.

The chief interest in the present case is the short right arm and leg, a feature which has occurred in two other cases only (Fairbank, 1949). X-rays, however, show the disease to be bilateral although the left side is much less affected. Unfortunately, in the other two cases no X-rays of the opposite side were available (Fairbank, personal communication), but in view of the findings in this case it is suggested that this is always a generalized bone disease.

In addition this is the only case traced where unilateral cataract has occurred although bilateral cataracts are a not infrequent association. Optic atrophy has also not been previously reported.

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Patchy Calcification in the Cerebrum. Presenting with Mental Deficiency and Petit Mal. ? Gliomatous Degeneration. ? Epiloia.—REGINALD LIGHTWOOD, M.D.

M. R., male, now aged 2 years 8 months; the first-born of healthy English parents. Birth-weight 5 lb. 7 oz. Appeared normal until 6 months old when there was a slight convulsive seizure (pale and rigid for two minutes); a similar attack occurred at eight months and subsequently there were fairly frequent attacks of *petit mal* type. Milestones: Raised head after 10 months; sat up about 14 months; crawled about 2 years. Incessant crying.

Family history.—Nothing significant. A child born subsequently is normal and the mother is now pregnant for the third time.

Investigations (at 2 years 7 months).—Physically normal but clearly mentally deficient, taking little notice, accepting anything without response and making senseless noises. Skull shows flattened and indented occiput, lateral part of frontal eminences rather poorly developed. Maximum circumference 18½ in.; intermeatal measurement 13 in. Eyes: Slight internal strabismus; slight pallor of optic discs; maculæ normal; no signs of retinitis or choroiditis. Nervous system normal apart from mental deficiency. Except in the cerebrum (Figs. 1 and 2) no other abnormal calcification shown by the X-rays. Tuberculin test (intradermal 1 : 1,000) negative; Casoni test negative.

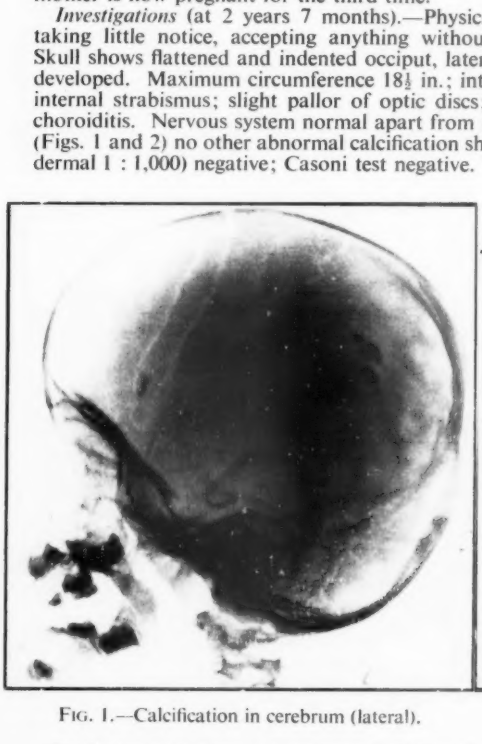

FIG. 1.—Calcification in cerebrum (lateral).

FIG. 2.—Calcification in cerebrum (A-P).

Further investigations.—The presence of intracerebral calcification suggested toxoplasmosis and it was learned that the mother when pregnant with this child attended a sick dog until it died of "distemper" or suspected encephalitis. Therefore tests for toxoplasmosis were done as follows:

Toxoplasma skin test 1 : 100 dilution	negative mother and child.
Toxoplasma cytoplasm modifying test	negative mother and child.
Toxoplasma complement fixation	negative mother and child.

X-ray interpretations of films (Dr. J. W. D. Bull).—The skull, which is perhaps slightly oxycephalic, is symmetrical and its size is about normal. The sutures are probably normal for the age but the possibility of some elevation of intracranial pressure is suggested by slight hammer markings of the posterior parietal and squamous occipital bones and flattening of the posterior part of the sella and some loss of its upper part.

Several irregular patches of calcification lie more or less symmetrically, in each temporal lobe just medial to the normal position of the anterior tips of the temporal horns, also in each parietal lobe, and there is a patch in the right frontal lobe and numerous tiny flakes scattered in the hemispheres.

Air ventriculography was not done.

Comment.—Intracranial calcifications may be divided into two groups (Caffey, 1945). *Physiological calcifications* occur, for example, in the choroid plexuses, falx cerebri, pineal body, Pacchionian bodies, and interclinoid and petroclinoid ligaments. The significance of such deposits of lime salt is not known but the subjects are in good health. *Pathological calcifications* may occur in neoplastic, traumatic, inflammatory, hæmorrhagic and

degenerative conditions. The neoplastic conditions mentioned by Caffey include astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, dermoid and teratoma. Also in angiomas, usually situated in the occipital lobes, calcification may occur giving a characteristic double tubular outline. None of these neoplastic causes is suggested by the clinical and radiological features of the present patient. On the other hand, epiloia cannot be excluded notwithstanding the absence of adenoma sebaceum. No history of trauma, bleeding, or any infection known to be a cause of intracranial calcification has been obtained; toxoplasmosis has apparently been ruled out; cysticercus and hydatid are not suggested by the X-ray appearances. Intracranial calcification, predominantly in the basal ganglia, may be a feature of increased or decreased activity of the parathyroid glands (Eaton, Camp and Love, 1939; Eaton and Haines, 1939). In the present patient there has been no tetany or X-ray evidence of bone disorder.

I am indebted to Dr. W. G. Wyllie for seeing the patient and for suggesting as a probable cause gliomatous degeneration of undetermined origin, with epiloia as an alternative.

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Visible Primary Tuberculosis.—DAVID MORRIS, M.R.C.P., D.C.H. (for MARY WILMERS, M.D., M.R.C.P.).

M. A., male, aged 4 years 4 months.

February 1950: First seen with vague ill-health for which no cause was found and recovery was spontaneous. Mantoux 1 : 1,000 negative.

May 1950: A "spot" appeared on the left cheek followed in a few days by left pre-auricular swelling and upper group of cervical glands in the anterior triangle.

June 1950: Attended hospital. The spot had now ulcerated, $\frac{1}{4}$ in. diameter, central crust, edges not indurated, and the glands were tender on pressure. Treated with sulphonamides and penicillin, without effect. Jelly test was positive. Mantoux 1 : 1,000 strongly positive. Admitted to Queen Elizabeth Hospital, Banstead. General condition good. No other physical abnormality.

Progress.—Ulcer became infected and the pre-auricular gland fluctuant. Aspirated, tubercle bacilli in the pus. Streptomycin $\frac{1}{2}$ gram in 1 c.c. inserted. The cervical glands have remained unchanged, the ulcer is healing and the pre-auricular gland is subsiding.

Investigations.—Chest X-ray clear. W.B.C. ranged from 10,000 to 17,000 with 50 to 60% lymphocytes. Gastric lavages for tubercle bacilli negative. E.S.R. never more than 17 mm./hr. No tubercle bacilli in the urine.

Mother was admitted to hospital with active pulmonary tuberculosis in September 1950.

FIG. 1.—Visible "primary" skin lesion with enlarged pre-auricular and cervical glands.

Primary Tuberculous Complex Left Eye.—D. Q. TROUNCE, M.D.

G. M., boy aged 12 years.

History.—Three weeks before admission developed a scanty discharge from left eye. Eye has never been painful but has sometimes itched. Two weeks before admission developed swelling in front of left ear, followed by swelling under left side of jaw. No cough. Appetite poor for about six months.

Family history.—Mother when aged 11 years had tuberculous cervical adenitis. Also at age of 17 years had tuberculous left tibia. She is quite well now. No known recent tuberculous contact.

Examination.—Left eye: Ptosis. Small papilla of granulation tissue on inner surface of outer angle of lower lid. Right eye: Normal.

Face and neck.—On the left side the pre-auricular lymph gland is enlarged to 1 in. in diameter. It is hard but not fixed to skin or deeper structures, not fluctuant, but slightly tender. Left tonsillar cervical and submandibular glands enlarged and slightly tender. Small shotty glands palpable in left posterior triangle.

Throat: Healthy.

All systems clinically normal.

Investigations.—Mantoux 1 : 1,000 negative. X-ray chest normal. B.S.R. (Westergren) 27 mm. in one hour. Blood picture: Hb 81%; W.B.C. 12,000 (neutros. 38%, lymphos. 58%, monos. 4%). Conjunctival swab: No cells or organisms. Ziehl-Neelsen film: No acid-fast bacilli seen. Culture sterile.

Treatment and progress.—9.10.50: Admitted. Bed rest. Has remained afebrile since admission. 12.10.50 started on streptomycin 800 mg. b.d. and PAS 2 grams b.d.

By 14.10.50 affected glands considerably smaller. By 16.10.50 left tonsillar and submandibular glands barely palpable. Pre-auricular gland very much smaller.

POSTSCRIPT.—Biopsy Report 1.12.50: The eyelid shows small follicles with eosinophilic centres which morphologically are similar to healing tubercles. There is a solitary giant cell of Langhans' type which makes tuberculosis very probable. The appearance of healing is very interesting as it is like that which is seen in streptomycin-treated tuberculosis.

Spontaneous Hypoglycæmia, ? Hepatogenous.—E. M. POULTON, M.R.C.P., D.P.H., D.C.H. (for E. HINDEN, M.D., M.R.C.P.).

Michael L., born April 21, 1947, one month premature, was the second of binovular twins. His mother was Rh-positive and W.R.-negative. His birth-weight was 3 lb. and he was deeply jaundiced with a greatly enlarged liver. His twin sister was healthy then and has remained so.

He was treated at Westminster Children's Hospital, with a tentative diagnosis of congenital stenosis of the bile-ducts. The liver returned slowly to normal size as the jaundice abated; this finally cleared at 6 months. At 2 years of age he developed bilateral cataracts. He has been slow in development and now at 3½ years he is just beginning to put sentences together.

In October 1949, when 2½ years old, he lapsed into coma when on his way to have an eye operation; he had fasted since the previous evening. Recovery was spontaneous. He again became unconscious in September 1950. His blood sugar on admission to hospital was 20 mg./100 ml. A subcutaneous drip infusion of 5% glucose was followed by recovery. His glucose tolerance curve was flat but within normal limits, as was the adrenaline response. A third coma occurred the day after discharge. On readmission the blood sugar was 31 mg., and recovery was spontaneous.

His sensitivity to insulin was tested (Hartmann, 1948). The fasting blood sugar was 52 mg.: then 3½ units of soluble insulin (i.e. ¼ unit/kilo. of body-weight) were injected. After 18 minutes, the blood sugar was 33 mg. and he was drowsy; after 32 minutes, he was very drowsy, and was given a sweetened drink; after 41 minutes, it was 19 mg. and he was in severe status epilepticus, and the experiment was ended. The lævulose tolerance curve was within normal limits.

The recurrent hypoglycæmia is thought to be due to failure of the damaged liver to make and store glycogen. The mental retardation may be due to his low blood sugar.

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Dr. Alex Russell considered that an intracranial lesion (either inflicting pressure-degeneration upon the anterior lobe of the pituitary or otherwise impairing its function) should be excluded as a basis for the profound hypoglycæmic incidents. Secondary hypoglycæmia during glucose and adrenaline tolerance tests and the insulin hypersensitivity together with some hypoglycæmia unresponsiveness lend support.

A craniopharyngioma or other relatively benign parapituitary tumour could be responsible and the disproportionate increase in head size in the presence of growth failure may be significant in this connexion. As part of the consequent multi-functional disturbance, a degree of hypoparathyroidism could account for the cataracts present.

Other hypothalamo-hypophyseal lesions, degenerative or inflammatory, could be responsible. Attention was drawn to Dr. Wilmers' case of cretinism wherein severe jaundice had persisted throughout the first five weeks of life, reappearing after an interval of several weeks, the liver meanwhile showing gross enlargement. At autopsy, following a fatal gastro-enteric episode at 3/12, Dr. France detected generalized cytomegalic inclusion body disease with massive involvement of thyroid cells and lesser concentrations in pituitary, liver, &c. Such pathogenesis for a uni- or polyglandular disorder should be kept in mind, especially in view of the similar history of severe jaundice in the case presented.

Dr. I. M. Anderson considered islet tumour of the pancreas might fit this case except for the history of jaundice in infancy and the extreme rarity of this condition in early childhood.

Dr. W. W. Payne suggested a high protein low sugar diet for this patient and emphasized that severe and prolonged hypoglycæmic attacks could produce lasting intellectual impairment.

Dr. E. Hinden replied that he was reluctant to postulate so rare a disease as islet tumour of the pancreas, when the undoubted liver damage could explain the condition. Inclusion disease of the endocrines was a most interesting and relevant suggestion, but he could see no way of substantiating or refuting this diagnosis.

Section of Laryngology

President—A. M. Zamora, M.Ch., F.R.C.S.

[*November* 3, 1950]

The Role of the Laryngologist in Bronchial Obstruction. [*Abridged*]

PRESIDENT'S ADDRESS

By A. M. Zamora, M.Ch., F.R.C.S.

In offering these few reflections on the subject of bronchial obstruction as it has presented itself to me over a period of more than twenty-five years, I realize that I can deal with only a small fragment of this great subject. There will be a minimum of statistics because, in such a wide review, statistics have only a limited and temporary value. The rarity of to-day is the commonplace of to-morrow, small numbers are apt to be dismissed as freaks and large numbers, though often the source of justifiable pride, have an inflationary air, tend to reduce the value of individual units and to transfer the emphasis from the subject of the statistic to the person who presents it. The few illustrative cases which I shall give are merely samples of small or large groups which have been referred to me in my hospital and private practice. I do not claim experience beyond that of any senior laryngologist who has been attached to a general hospital and to a hospital for diseases of the chest.

From my earliest days this subject has interested me and, like the late Ewart Martin, that great champion of endoscopy, I paid a visit to Chevalier Jackson's clinic in 1919. Perhaps in its modern form, bronchoscopy owes most to the brilliant mechanical mind of Chevalier Jackson and to his attractive and forceful methods of presenting the subject. In his Semon Lecture, Ewart Martin (1949) clearly showed that endoscopy was first developed by laryngologists. The sequence is familiar to all—Killian, Brünings, Jackson, Mosher, Negus and others. The stimulus was slow in reaching England and the technique was not taken seriously, except by the laryngologists, and was often made the subject of tolerant banter. It eventually passed beyond this stage, and Negus, with his inventive mind, gave the biggest impetus to British endoscopists who are now numerous and skilled. Indeed, so fruitful is the endoscopic approach, that the manœuvre has spilt over to chest surgeons and physicians and now there is some difficulty in allotting cases, a situation which needs consideration.

It is the common practice in hospitals in this country to have the laryngologist responsible for treatment of all cases of swallowed or inhaled foreign bodies and generally for carrying out endoscopic examinations requested by physicians and surgeons. In a few centres the physicians do their own bronchoscopies and some limited non-surgical bronchoscopic treatment. Surgical treatment, if needed in such cases, has to be delegated to the laryngologist or chest surgeon. The chest surgeons, very rightly, insist on doing their own bronchoscopies and have notably advanced the science of endoscopy (Brock, 1946, and many other authors).

Clearly, these examinations may reveal a variety of conditions, some within the scope of purely endoscopic treatment and some obviously beyond it. It is for this reason that I give this brief account of the laryngologist's side, hoping that it may lead to the implementing of what I think may have been Ewart Martin's purpose—the stimulation of interest in the subject and the more concise definition of the role of the laryngologist. The present practice entails much duplication of work which, though it may bring bronchoscopic experience, is clearly not in the patient's interest.

Before considering my few chosen cases, I think it fitting to acknowledge the great debt which the average endoscopist owes to those workers who have brought about a progressive simplification and increasing efficiency in the instruments, from the ingenious but vulnerable Killian's telescopic tubes with Brünings' lighting, with which I started, to the present-day Negus apparatus with valuable tapering and simple lighting.

Foreign Bodies

Many foreign bodies have been removed in my Clinic, but although their removal needs all the refinements of endoscopic technique, I shall not discuss this subject because it appears that, at present, there is no wish to remove from the laryngologists the responsibility for these cases.

Infective Group

Over the years, a large number of these cases have been referred to me.

In *true bronchiectasis*, bronchoscopic suction can be a good palliative in cases where postural drainage and other measures are insufficient or have failed, and it may be a good preparation for lobectomy by improving the patient's stamina. Curative treatment lies with the chest surgeon. The early hopes of good results with bronchial lavage have not been fulfilled and this technique is tending to be discarded.

In *lung abscess* there is no doubt that effective drainage can be promoted or accelerated by bronchoscopy in the early stages. Those cases that do not clear quickly and completely both clinically and radiologically generally go eventually to the chest surgeon for external drainage or more severe measures.

My experience does not bear out the claims that have occasionally been put forward that actual access to the abscess cavity is possible with a bronchoscope. This is, I think, a very rare occurrence.

Bronchoscopy in these cases must, therefore, be rated as an aid to natural resolution, but once this has failed, it can play no important part.

Cases Associated with Anterior Poliomyelitis

At the Royal National Orthopædic Hospital, Country Branch, among the large number of children treated, there have been many cases of extensive paralysis from anterior poliomyelitis. Some of these have considerable intercostal involvement, but have adequate respiratory power for their restricted lives. They are, however, largely dependent on accessory muscles of respiration, these in some instances also partially out of action. The reserve of respiratory power is therefore very limited and a minor infection becomes lethal. The urgency of these cases is astonishing. Within a short time they are labouring under the greatest difficulties and it is imperative to put them in a Drinker respirator. Spontaneous voiding of secretions is not possible and, unless bronchoscopic suction is applied, they certainly die. Bronchoscopy may have to be done while they are in the iron lung, a most difficult procedure, or it may be possible to get them out and use a Bragg-Paul apparatus. The condition of these patients makes every case an alarming one.

(Two typical cases treated successfully with bronchoscopic suction were described and serial X-rays shown.)

There are certain points about these cases which are difficult to fit in with the purely mechanical and accepted views of causation of atelectasis. In the two cases recorded and, indeed, in most, there is little relation between the amount of secretion present and the gravity of the atelectasis, and in this regard they come into the category of some post-anæsthetic cases and so-called "unresolved pneumonias". Everybody is now familiar with Chevalier Jackson's conception of the various possible valvular effects of bronchial obstruction which may produce either emphysema or atelectasis depending on the position and nature of the obstruction. The early and therefore rarely described obstructive emphysema has been emphasized by some—notably Gerlings (1939). Far more commonly one sees the obstructive atelectasis. There is no doubt that a complete obstruction will lead eventually to atelectasis, but all bronchoscopists must have been impressed by the atelectatic changes which are sometimes found without bronchial plugs and quickly relieved by removal of insignificant amounts of secretion. Now, the considerable raising of the diaphragm, the approximation of ribs and displacement of mediastinum are events which need for their causation far greater pressures than those which could be exerted by elasticity of lung tissue alone. The absorption of air, it has been stated, also needs greater pressure. Atelectasis can occur after thoracic or abdominal contusions, expecially those affecting the nerve plexuses. It can happen in response to acetylcholine or even with rough instrumentation.

These are facts which are brought forward by Xalabarder of Barcelona (1949) to support his theory that atelectasis is not in all cases a pure collapse, and that there is a physiological reflex whose trigger point is uncertain. This is probably situated in the larger bronchi, and can cause an active contraction of the muscle tissue of the lung; it is controlled by the autonomic nervous system. This theory has much to support it. Research work which would help to localize the sensitive areas would be of great value. It does, perhaps, correct the tendency to overemphasize the purely mechanical aspect which results from Jackson's work.

Tuberculosis

The old reluctance to bronchoscope tuberculous patients has almost gone. It is now in a stage of rapid development as a means of reaching localized bronchial lesions and as a guide to treatment. Important as the subject is, it is still largely in the experimental stage.

NON-INFECTIVE GROUP

Hypertrophic cases.—The lining of the trachea and bronchi has a tendency to respond with marked hypertrophy to certain stimuli, and to tolerate others. Trauma and vegetable foreign bodes are unacceptable and lead to swelling which tends to become polypoid and pendulous.

I have twice removed pedicled masses from the subglottic region caused by intratracheal intubation. These were large enough to cause nearly complete intermittent obstruction.

(A case was described in detail of a pedunculated granuloma removed from the bronchus of a boy and caused by a vegetable foreign body.)

Papilloma.—Considered by the author as a sort of intermediate state between hyperplasia and neoplasia.

(A case of multiple papillomata affecting larynx and trachea with a large parent growth in the left bronchus and successfully treated by endoscopic removal was described. The patient has done twenty years' full work since his first bronchoscopy and is now in robust health.)

Neoplastic group.—By far the largest number of cases of bronchial neoplasm are, unfortunately, malignant. Here the laryngologist's role is limited diagnosis or temporary canalization, palliative or in preparation for chest surgery.

Benign group.—The recognition of the occurrence of innocent tumours in the bronchi is relatively recent history. Patterson (1930) found only 26 cases in the literature. Those were early days of bronchoscopy. The increasing use of this method of investigation has brought to light a much larger number of cases, but still reports of proven cases are distinctly rare. It is, I think, certain that they occur much more frequently than is apparent from the reports and that they are often classified under the heading of their secondary effects. Fibromas, chondromas, lipomas, hæmangiomas and adenomas are described. The histological problems are not yet solved and it is difficult to isolate some groups from others.

I have not seen a lipoma, but have met with all the others.

Chondroma I have seen only in relation to laryngeal cartilages. They have been the subject of many monographs, notably the early studies by StClair Thomson and Irwin Moore.

Fibromas are rare. The following example is rather unique:

C. W., an accountant, aged 59, seen with Dr. Stott (now Sir Arnold Stott), in 1931. History was of increasing shortness of breath for six months. Winter cough. Scanty sputum. Occasional blood clots, and gradual moderate loss of weight. When he was referred to me he had a very severe inspiratory stridor. Bronchoscopy showed a normal larynx and a smooth rounded mass at the lower end of the trachea, apparently almost completely occluding the airway; moving slightly on respiration and reflecting the light in patches. The uneven movement of these reflections suggested that the mass might have a pedicle attached to the front of the trachea. This was found, the growth avulsed and delivered through the widely stretched larynx. There was immediate and lasting relief of all symptoms. There had been no X-ray evidence of pulmonary disease—an interesting example of the capricious effects of obstruction in causing atelectasis. This patient died seven years later without any sign of recurrence of bronchial symptoms. He died of Bright's Disease. Histologically it was a cellular fibroma.

This was a case for purely endoscopic treatment.

HÆMANGIOMA AND HÆMANGIO-ENDOTHELIOMA

Case.—Mrs. W., a retired Theatre Sister, developed shortness of breath and dysphagia. On examination a reddish mass was seen on the right arytenoid and spreading down over the vocal process well into the subglottic region. Two attempts at removal and diathermy were followed by quick recurrence and alarmingly rapid growth. In desperation I asked my colleague Mr. Anthony Green if he could help with deep X-rays. This was successful and, seen in July 1950, she was quite free from recurrence and perfectly well.

I have seen several other cases of this type in the trachea and bronchi, a possible cause for hæmoptysis which must be kept in mind.

A case seen with Dr. R. R. Trail had a flat hæmangioma at the tracheal bifurcation. Severe hæmoptyses were stopped by chemical cautery.

This type is of special interest because of the possibility of severe bleeding. The interesting case recently reported by Sharp (1949) of dyspnœa in an infant caused by a tracheal hæmangioma and necessitating a bold and difficult external operation can be cited as an instance of the possibly embarrassing situation in which a physician might find himself during a diagnostic bronchoscopy.

The successful treatment by deep X-ray of the case I have described is worth recording. Two similar cases reported long ago by Cann (1938) were diagnosed histologically as "basal-celled carcinoma of the trachea" by distinguished pathologists, with the comment that they had the appearance of a mixed parotid tumour. These, I think, would now be regarded as being clearly related to the present group. They were also successfully treated with deep X-rays. In accessible places, therefore, this should be the treatment of choice.

Adenoma.—Here we reach an interesting and controversial topic, for these tumours form a group of unusual characters and the line between innocence and malignancy is not yet clearly defined.

As far back as 1930 I became interested in lung adenomas, the commonest of the "innocent" bronchial tumours described. About that time, several of these cases were referred to me by the physicians of the Royal Chest Hospital and later formed the subject of a short paper (1937) by myself and Dr. Nora Schuster, Pathologist to the Hospital, to whom, and to Dr. P. O. Ellison, I am now indebted for great help with the histological part of this present communication.

After these many years it does not seem necessary to alter the general clinical and pathological description, but a radical change has appeared in the conception of their treatment, on account of the prodigious development of the surgery of the chest. The annotation of many cases in recent years, particularly in America, has brought out some new facts but has not yet brought a final decision as to the true nature of these tumours.

I ask leave to recount one of my early cases because it is truly typical and because its after-history is of interest.

Miss W., aged 30, an active athletic woman, referred to me by Dr. Eric Bellingham Smith.

Symptoms began in 1934 but diagnosis was not made until 1936 when she came under the care of Dr. Bellingham Smith. She had severe intermittent attacks of breathlessness, hæmoptysis, cough and wheezing. The general condition was fairly good. The physical signs were of great complexity and she had, in her first two years of illness, been labelled under a variety of venerable diagnostic headings.

X-ray showed complete collapse of left lung; raised diaphragm; compensatory emphysema of right lung and obstruction of left bronchus.

Bronchoscopy showed a mass at distal part of left bronchus, suggestive of adenoma. The polypoid rounded pinkish appearance is now familiar. In those early days it was an exciting finding. On section it proved to be an adenoma.

At a second bronchoscopy as much of the tumour as possible was removed by forceps and radon seeds were sown round the growth. After a febrile episode, she began to improve considerably and her doctor sent good reports. She could not, however, be induced to come up again for further bronchoscopy. The war broke the continuity of the record but I know that during that time she had an empyema and that eventually she died distressfully of asphyxia, in 1947 (thirteen years after the first symptom), in a manner suggesting to Dr. Bellingham Smith the possibility of a malignant change.

No post-mortem specimen of this case is available, but a picture made from another, very similar case, of Dr. Buckley Sharpe's illustrates the morbid anatomy of such growth. Tumour blocks the opening of the bronchus (upper lobe) and extends along it, and bulges the wall of the main bronchus. This patient died of acute lung sepsis before an attempt was made to clear the bronchus.

Owing to the bombing of the Royal Chest Hospital and destruction of records it has been difficult to trace the cases reported prior to 1937, but I know that one of these died in 1949 having developed what Dr. James Maxwell describes as a "curious constrictive pericarditis". Two others are still alive but have both had lung infections, one an empyema and the other a lung abscess successfully drained.

Other cases have turned up at rare intervals.

Finally I will bring in one of these seen three months ago in which bronchoscopy was done to try and discover the cause of a right upper lobe opacity. This showed, in the course of examination, a round bud-like eminence on the medial wall of the lowest part of the right main bronchus, which I removed. Obviously it had no direct relation to the lesion in the upper lobe. The section was described by one pathologist as an adenoma and by another as a "teaser" containing mostly normal tissue but in one part resembling a papilliferous tumour.

From such cases and specimens I have tried to draw some personal conclusions.

Trying to fit in my observations with the writings of experts I have come to the view that there is a definite clinical and pathological entity which can fairly be described as a vascular adenoma of the bronchus, a tumour of slow growth, with powers of local infiltration only and no tendency to metastases. The histological picture is fairly constant in a number of cases and the standard type is that shown in the case of Miss W. The clinical picture is of the greatest variety because it depends on the many possible obstructive and infective secondary effects, but common symptoms are hæmoptysis and cough in a youngish person, generally a woman.

Recently, evidence has been brought forward that:

(1) Adenomas may be multiple or be associated with adenomas in other parts of the body (Howes, 1948).

(2) They may occur in the outer periphery of the lung and be out of reach of the bronchoscope and in the region where no mucous glands are said to exist (Maier and Fischer, 1947).

(3) They may become malignant (Graham and Womack, 1945).

This last is the main point to consider. It is, in my opinion, still debatable. There seems no doubt that certain cases acquire malignancy, but there is a possibility that the histologists may yet be able to isolate a picture which can be definitely labelled "innocent". Many of these tumours have no accepted histological character of malignancy when first seen. Many patients have had symptoms for a number of years and if malignant change occurs it may be so slow that there is time for a normal span of life.

These tumours force one to reflect upon the value of biopsy—a question which will be discussed on March 2, 1951. They are perhaps examples of the importance of being guided by what the late Professor John Ryle called "the study of the Natural History of Disease"—rather than by purely technical scientific aids.

There are two main theories as to the origin of these tumours: (1) They are derived from mucous glands; (2) They are the result of abnormality in development.

I incline to accept the theory of developmental anomaly. Adenomas have been described in regions of the lung devoid of mucous glands. The development of the lungs by repeated budding from the primitive pharynx which is said to go on to the 7th year of life (Keith, 1948) makes it easy to imagine that an occasional aberration may occur resulting in vestigial masses. The last case described may well have been one of these. Such aberrant masses may take the form of vestigial accessory lobes with normal tissues or they may preserve to some variable extent their embryonic structure. The resemblance between the tumours we are considering and fœtal lung tissue is marked.

It is clear, therefore, from these considerations (namely, the possibility of malignant change, occasional occurrence beyond the reach of the bronchoscope, and difficulty in eradicating adequately by endoscopic methods any but the earliest endobronchial adenomas) that we pass, as laryngologists, beyond the scope of our usefulness in treatment, and that the only hope for such patients is in the hands of the chest surgeon. In his hands the prognosis appears to be very fair. There is no doubt, however, that in cases which cannot support, or will not accept, major chest surgery, repeated endobronchial treatment may be of the greatest help.

We must acknowledge, therefore, that the bronchoscopic method originated by the laryngologists has brought to light a large number of different conditions in the lung, but that, from the point of view of treatment, they form distinct groups:

(1) Amenable to purely endoscopic treatment and comprising early and reversible infective changes (including certain bronchial tuberculous lesions), the purely benign growths, and some accessible adenomas.

(2) Cases needing palliative or preparatory canalization.

(3) Cases which are beyond the scope of the laryngologist. The major chest infections—bronchiectasis, established lung abscess, certain chosen tuberculous cases, the proven and the doubtfully malignant growths. These are in the sphere of the chest surgeon.

All these cases have to be bronchoscoped.

To whom are they to be referred, and who, after diagnosis, is to treat them? At the present time there is some confusion in this respect.

There is a very obvious solution to this difficulty in the widespread establishment of endoscopic clinics in which the chest surgeon, chest physician and laryngologist work in close co-operation. There are only a few such clinics. In such clinics the laryngologist has a strong claim to play the major role in examinations and treatment of purely endoscopic cases. The result will certainly be a great increase in efficiency, a saving of time, and a real possibility of early diagnosis which is the cardinal need for good results with less radical surgery.

There will be very few who will not praise and admire the successes of radical surgery which, by the solution of an infinity of technical problems, has made it possible to remove with relative impunity many of the major organs of the body. There will, I think, be even fewer who will not hope that these successes, brilliant though they are, will turn out to be interim measures awaiting a time when life can be saved and function restored without major ablations. I think that, with few exceptions, the type of mind of members of this Section *is* conservative (Gill-Carey, 1944; Owen, 1950). The eternal cry is for early diagnosis. In the lungs this possibility may rest with a great increase in the use of the bronchoscope by properly organized teams co-operating with one another and spread over the country.

(The case descriptions included X-ray films and histological sections—which may appear with the full paper in *Journal of Laryngology and Otology*.)

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Mr. V. E. Negus thought there was considerable reason for anxiety in the future, because of gradual loss of material. As laryngologists it was their duty to educate the younger men, many of whom had to go into the towns and cities of this land, where they would be expected to carry out many endoscopic procedures, particularly those connected with the removal of foreign bodies.

Quite obviously it was important for anyone dealing with affections of the respiratory tract to study all parts of the tract. Rhinologists and laryngologists should not confine themselves to the upper part, that is, the nose, the sinuses, the pharynx and the larynx, but they should have some appreciation of what went on further down. It was undesirable to separate the respiratory tract in an arbitrary manner. It was important that the physician dealing with diseases of the chest should see for himself by bronchoscopy, and similarly for the surgeon who was going to operate on such cases. It could not be suggested, therefore, that bronchoscopy must stay exclusively in the hands of the laryngologist, but without some arrangement it would leave their hands.

The chest physician's work was confined mainly to bronchoscopy, but to separate bronchoscopy from laryngoscopy and œsophagoscopy was a mistake. If the physician did not operate himself, he could not be expected to go at the convenience of the laryngologist or the thoracic surgeon to see his cases; there must therefore be some better arrangement. The thoracic surgeon did a great deal of endoscopic work, but in the past more in the bronchi than in the œsophagus. As work increased it might be difficult for him to do it all and in the future he might be glad to be relieved of some of the work which did not concern him so directly, that is, where there was no necessity of an external operation.

The thoracic surgeon must obviously see for himself; it would be equally unnatural to suggest to the urologist, for example, that he should have someone else to carry out cystoscopy. Unfortunately thoracic surgeons were not distributed over the country so evenly as were laryngologists and it would be unfortunate if a thoracic surgeon were expected to do all the endoscopic work in the many centres where there was available an ear, nose and throat surgeon. It would be more convenient and advantageous if some of the work could be carried on by the laryngologist.

The laryngologist had the daily necessity of dealing with the respiratory tract and there was a very wide distribution of such specialists over the country as a whole. He had a good moderating influence in this branch of work, as for example in the treatment of cardiospasm. Instead of opening the stomach, putting in a hand and dilating the œsophagus, the laryngologist treated the disease by the simpler method of peroral dilatation. Some credit could also be taken for the cure of a certain number of patients with bronchial abscess by bronchoscopic aspiration, without the necessity of external drainage. He knew that nowadays thoracic surgeons and physicians would, however, make every use they could of the simpler methods which were least likely to upset the patient.

It was very much better for the endoscopic clinic to deal with all types of work, that is to say, laryngoscopy, pharyngoscopy, bronchoscopy, and œsophagoscopy. It was a great pity to separate them, as one used the same techniques and the same type of instruments; very often a double examination had to be made, as, for example, to see whether it were possible for a radical operation to be performed for carcinoma of the œsophagus, by looking for evidence of mediastinal glands or infiltration of the bronchi, and to observe whether paralysis of the larynx were present. The laryngologist should not be asked to deal with foreign bodies without a great deal of experience in other types of endoscopic work; 95% of endoscopic examinations for various diseases and 5% for foreign bodies was about the right proportion. Thereby one learned one's way about, the theatre staff became used to the work, there was an adequate range of instruments. To deal with foreign bodies only was not at all a good way to work. Incidentally the laryngologist had an advantage over others because he was used to working most of the time with only one eye.

The President had suggested that this work was so much in a common field that it would be a great advantage if they did not all go their own independent way. A combined endoscopic clinic for training purposes would be advantageous. There would be the great advantage of frequent contact and discussion with colleagues; and it would give excellent opportunities and adequate material for the education of younger men.

Mr. C. Price Thomas said that he was entirely in agreement with both the President and Mr. Negus as to the necessity for closer co-operation between those working in the field of bronchoscopy. He favoured the establishment of joint clinics for training young clinicians, surgeons, laryngologists, and physicians, in this particular branch.

Though the technique itself was simple, judgment could only come with experience. Bronchoscopy had two aspects, therapeutic and diagnostic, and it was the latter which was of supreme importance to the thoracic surgeon. The report on bronchoscopic findings should be made in anatomical terms. At present, the laryngologist was primarily concerned with establishing a diagnosis, but the surgeon was also concerned with the presence or absence of signs of inoperability, without which criteria the report was almost useless to the surgeon. Joint training in this field only could lead to uniformity in such matters, but it had a further rich reward in that persons so trained would have the advantage of contact during their formative years with other workers in this field and hence an enlarging of their clinical horizon. To illustrate this latter point, he referred to the group of tumours

designated adenoma of the bronchus. The laryngologists, heretofore, had submitted these cases to bronchoscopic removal, and although he agreed that they were essentially benign, the majority of cases were quite unsuitable for such treatment for the tumours were often both endo- and extra-bronchial, they were often broadly sessile, or in such a position as to be inaccessible by bronchoscopy. He had done a local resection of the tumour with a portion of the bronchial wall successfully in 5 cases, afterwards reconstructing the bronchus, thus avoiding the necessity of removing any lung tissue. The latter procedure was rarely possible as usually the degree of destruction beyond the tumour by inflammation was so great as to make resection imperative, for the latter was the inevitable cause of death in untreated cases. He disagreed with Graham who considered these tumours to be essentially malignant, as he had never seen a recurrence after resection in such cases, although it could not be denied that certain carcinomas may have originated as adenomas.

A too assiduous persistence in attempts at bronchoscopic removal should be avoided, as not being without considerable risk, and such cases could be satisfactorily dealt with by bronchotomy with no greater risk than appendicectomy and much less discomfort to the patient.

He hoped that the formation of joint training clinics would become a reality as they could confer only benefit on the physician, the laryngologist and the surgeon and last, but by no means least, their patients.

Dr. James L. Livingstone said that some years ago, during the period of ten days, he knew of 3 cases who died as a result of bronchoscopy, all from an overdose of local anæsthetic. He also recollected a man with a carcinoma of the trachea who was bronchoscoped by a registrar who failed to look at the trachea when passing the instrument. Whoever carried out the procedure therefore should have enough experience to be really expert at it.

Bronchoscopy was used as a routine method of examination by several specialists besides the laryngologist and the thoracic surgeon, for example anæsthetists, physicians at chest hospitals, both for routine work and for research on respiratory physiology. In hospitals for tuberculous children bronchoscopy was used extensively.

Perhaps the chest physician was the best person to refer a case for bronchoscopy to the specialist concerned.

He entirely agreed with Mr. Negus and Mr. Price Thomas that there should be chest centres for post-graduate training, where all types of respiratory diseases were treated and where regular clinical meetings, attended by all members of the staff, were held. It was important that the younger men in training should see all types of chest disease and gain experience in bronchoscopy and other methods of investigation. He would associate himself with Mr. Price Thomas in wondering whether special bronchoscopy clinics in different regions were really practical as it was so difficult to get various people together at the same time, and bronchoscopy was in fact only one of the special investigations required in diseases of the respiratory tract.

The President said that it had emerged from the discussion that in the formation of bronchoscopic clinics and the training of endoscopists pooling of experience and organization were desirable.

The chest surgeons had practically been handed over the treatment of adenomas because, without bronchoscopic clinics, it was impossible for the bronchoscopist to deal consistently with these tumours. It was the very fact that these centres were not available which turned them into major surgical cases, and he still hoped that one day it might be possible by a great development in the technique to be able to get tumours at an early stage and treat them.

He agreed with Dr. J. L. Livingstone that the physician was the man who should choose the method of treatment. The head of such a clinic should be the physician. Dr. Livingstone was fortunate because he had got his endoscopic clinic at the highest point of development but very few people in the country were so favourably placed. It was for that reason that the speaker was still of opinion that as there was now a central organization, and matters of expense were not quite so urgent, it might be possible to have regional centres where this important work could be carried out.

Section of Dermatology

President—W. N. GOLDSMITH, M.D., F.R.C.P.

[*October* 19, 1950]

Multiple Lymphocytomata in Association With Diabetes Mellitus.—C. H. WHITTLE, M.D., and A. LYELL, M.D.

Mrs. A. R., aged 63.

The patient was first seen one year ago with a monilial vaginitis which proved to be a complication of diabetes mellitus. She also had mauve nodules symmetrically distributed over the upper arms and chest which she said had appeared suddenly one year previously, one week after an attack of diarrhœa, and had persisted.

The nodules, of which there are several hundred, are up to 5 mm. in diameter, and are thickest on the posterior axillary folds, the backs of the upper arms and over the shoulder blades but are also present on the forearms, neck, buttocks, breasts, abdomen and loins. The feet and hands are spared, but there have been a few nodules on the face. The nodules are slightly tender, and cause some itching and burning. They are more prominent in the evening. On diascopy a faint brownish stain remains.

Two excised nodules were examined by Dr. A. M. Barrett, who found a similar histology in each, namely a uniform focus of lymphocytes in the mid-corium, extending up to the sub-papillary layer. At the periphery there was some perivascular infiltration, where the uniformity of the cells was not maintained.

The diabetes mellitus has been controlled, initially by diet and insulin and latterly by diet alone; the vaginitis cleared without local treatment, but the nodules remain unaltered. The patient is in excellent health, and her weight has been steady at 150 lb. for a year.

Special investigations.—Wassermann reaction negative.

Blood cholesterol 135 mg.%.

Blood counts: January 2, 1950: W.B.C. 10,000; lymphos. 20·5%. August 2, 1950: W.B.C. 13,000; lymphos. 22%.

Histological fat stain negative.

Histologically the nodules consist of uniform foci of lymphocytes without any trace of follicle formation as was found in the cases described by Hallam and Vickers (1939) and Hellier (1939). The histological picture of the present case is more like the skin infiltrations seen in lymphatic leukaemia, but the excellent general health of the patient, her steady weight, normal blood counts and absence of lymphadenopathy or splenomegaly are all against this interpretation.

We do not consider that this patient has a leukæmia; nor has she that type of lymphocytoma where there is lymphadenoid formation. We have had difficulty in naming this striking eruption, of which we have found no other example in the literature. But since the lymphadenoid type of lymphocytoma, when multiple, is not symmetrical (Bäfverstedt, 1943) we should perhaps have called this case symmetrical rather than multiple lymphocytomata.

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POSTSCRIPT.—The patient has now (March 1951) developed a splenomegaly and considerable painful enlargement of the epitrochlear glands.—A. L.

Dr. Henry Haber: The section reveals a dense infiltrate within the cutis. There are also rows of cells infiltrating in between the collagenous bundles. The infiltration consists of uniform cells of the lymphocytic type. The histological diagnosis should be therefore lymphocytic reticulosis. This case might develop leukæmia one day. The histology of lymphocytoma is in some respects different. It consists of a hyperplasia of lymphoreticular tissue with germ centres and an admixture of plasma and eosinophilic cells. The picture resembles that of a mild lymphadenitis. Bäfverstedt, B. (1943, *Acta derm.-venereol., Stockh.*, **24**, Suppl. XI), has clearly defined both conditions, both clinically and histologically.

Dr. F. F. Hellier: I would agree with Dr. Haber and would stress the absence here of the follicular arrangement which one sees in lymphocytoma. There is a feeling that a lymphatic leukæmia must start in a lymph gland, but it can start in the lymphoid tissue of the skin. It may remain localized for years and we can talk of a leukæmia cutis in a true sense. It may be a long time before there are any blood changes. I think this case will ultimately develop into a frank leukæmia.

Dr. Daphne Anderson: I will support the previous speakers. I have been following a rather similar case where the patient showed more reddish-mauve nodules on the skin. During four years her general health has remained excellent but recently she has developed widespread enlarged glands and an enlarged spleen. A diagnosis of benign lymphocytoma was made initially and has now been changed to Follicular Lymphoblastic Reticulosis.

Dr. C. H. Whittle: We are aware of the possibility that this case may show leukæmic manifestations later on. I would like to ask Dr. Oliver or other members who have had experience of these cases whether they would expect at this stage, or at any stage when there is no change in the blood, to find any satisfactory evidence of aleukæmic leukæmia in the bone-marrow?

Dr. J. O. Oliver: I think it extremely unlikely that a bone-marrow biopsy would show what would be described as *satisfactory* evidence of leukæmia in its aleukæmic stage if the peripheral blood showed no change. There might be a little shift of the lymphocyte picture in the bone-marrow, making it suggestive, but one could not accept a satisfactory differential diagnosis from the bone-marrow at this stage.

An Unusual Mycotic Infection.—P. D. SAMMAN, M.D., M.R.C.P. (for F. R. BETTLEY, M.D., F.R.C.P.).

Mrs. E., aged 64.

History.—For twelve to thirteen years she has suffered from itching and pigmentation of both forearms, and for about four years the finger nails have been deformed. Pigmentation of her face appeared several years ago and recently has become more pronounced.

The patient works as a cleaner and the condition does not interfere with her work. Her husband died six years ago of carcinoma of the lung. There were no children but two ectopic pregnancies were terminated by operations three years apart. Except for these operations and an appendicectomy the patient has always been fit. She has always lived in this country.

Examination.—There is pigmentation of the whole of the forearms with some telangiectasia and lichenification. The upper margin, when first seen, was sharply delineated but with treatment this can be seen to be receding. On the front of the wrists there are small areas of normal skin but with islands of involved tissue included. The palms and the backs of the hands are dry and scaly but pigmentation is not prominent. The nails of all fingers, except the index fingers, are infected; they are brittle and there is granular debris beneath them.

The feet, toe nails and lower legs are involved to a much smaller degree but the fungus is readily obtained from them.

The lower half of the face, especially around the mouth, shows pigmentation of a dark brown to black colour; there is here no overlying fungus infection.

General examination revealed no evidence of luetic infection elsewhere.

Investigations.—Fungus was found on the skin and in the nails of hands and feet and on the pigmented areas of the forearms.

Culture: *Trichophyton sulphureum.* This was prepared in the mycology department of St. John's Hospital for Diseases of the Skin, London.

Wassermann reaction positive; Kahn strongly positive.

Histology (Dr. H. Haber): The epidermis shows marked hyperkeratosis of the basket-weave type, patchy acanthosis and fusing of rete pegs and œdema of the basal cell layer in many places. The upper and mid-cutis exhibits many newly formed blood vessels and a marked infiltration consisting of lymphocytes and plasma cells. Situated mainly at the base of the infiltration there are numerous histiocytes containing blood pigment. (The biopsy was taken from the forearm.)

Comment.—Dr. N. C. Dey immediately recognized this case as similar to a number he had seen at the School of Tropical Medicine, Calcutta, and called " Melano-leucoderma". All his cases had a positive blood Wassermann reaction and about half were associated with the fungus infection, the organism being, however, *Trichophyton rubrum*. He considers the condition to be a valuable diagnostic sign of previous luetic infection.

Dr. P. J. Feeny: I would suggest that the fungus has nothing to do with the pigmentation, and that it is purely incidental. She has a fungus infiltration in the nails.

Dr. A. C. Roxburgh: I understand that the pigment was iron-containing on the limbs, but was it also iron-containing on the face or was it melanin there?

Dr. F. F. Hellier: She has not got that bluish slaty look which is so characteristic of iron pigmentation; there is obvious melanin pigmentati on the face. She was taking some medicine for a year for her eyes; I do not know what the medicine was but I wondered if she was taking any arsenic; if so, possibly the irritation of the fungus infection may have localized the pigmentation. There is a recent article by Bureau, Y., Rinckenbach and Barrière, H. (1950, *Ann. Derm. Syph.*, **10**, 385) who had the opportunity of seeing people who had taken wine laced with arsenic for a considerable period; some of their pictures are not unlike this patient's hands.

Dr. H. J. Wallace: Does anti-syphilitic treatment have any effect on this disorder?

Dr. P. D. Samman: I do not think the patient has been taking arsenic. I think the pigment on the face is melanin. We hope to get a biopsy from it presently. The arm has been treated with Whitfield's ointment and she has been given potassium iodide and mercury. The condition has improved, but whether the improvement is due to the ointment or the medicine I do not know.

Dr. Dey says that the cases in India are given anti-syphilitic treatment.

POSTSCRIPT (17.11.50).—I have been unable to obtain evidence of the patient having taken arsenic in the past.

A biopsy from the face has been prepared and it shows a different histology from the arm. The infiltration is much less marked and the pigment is melanin.

Chronic Vesicular Impetigo of the Trunk (Two Cases).—D. S. WILKINSON, M.D.

I. Mrs. E. L., aged 53. Housewife.

This patient was in good health until, in 1934 when pregnant, she developed pains in the smaller joints. These have continued with a distribution and undulant course suggestive of mild rheumatoid arthritis, though there is little confirmatory evidence of this. A more severe attack occurred in 1941 and about that time she developed a group of blisters quite suddenly on the right shoulder. These died away, but recurred on both shoulders next spring. They gradually extended until, in 1946, a generalized bullous eruption supervened. This subsided (after a course of penicillin), but the blisters appeared again the following spring "after the shock of a fall".

Since then she has had a constant eruption of small superficial vesicles, chiefly around the flexures of the body and the proximal parts of the limbs. The hands, feet, face and mucous membranes have not been affected; the eruption has become more extensive during the last two years. There has been no irritation. The eruption was worse at the time of her menopause five years ago.

Salicylates and "Veganin" have been taken from time to time, but their omission makes no difference to the rash. She has in the past taken a phenolphthalein laxative, but not in recent months.

Present appearance.—A well-nourished, healthy-looking woman who shows an eruption scattered over most of the trunk and proximal parts of the limbs. This consists of a series of individual lesions, with normal skin between. A small vesico-pustule appears, surrounded by a pink areola. This rarely becomes larger than a centimetre in diameter, but after two or three days becomes hæmorrhagic and then shrinks, leaving a brownish scab which separates, to show an area of discoloured (but not pigmented) skin. The lesions are not herpetiform, but do appear to arise in groups, or extend over an area centripetally.

On the legs, several lesions have coalesced and an area of skin has broken down to form a superficial ulcer in recent weeks.

Investigations.—General clinical examination has shown no abnormality, except for obesity, and slight swelling in some small joints. There is X-ray evidence of apical infection in the root of one tooth.

W.R. and Kahn negative.
Blood count (28.4.50): Hb 85%.
W.B.C. 6,000—normal differential.
E.S.R. 1949 34 mm./in 1 hour.
1950 22 mm./in 1 hour.

Serum calcium 9 mg./100 ml.
Serum potassium 17 mg./100 ml.
Serum uric acid 3·8 mg./100 ml.
Alk. phosphatase 5 (K-A) units.

X-ray: Knee-joints: "changes of osteo-arthritis." Hands: no abnormality. Teeth: "apical infection at one root."

Skin biopsy (Dr. I. W. Whimster).—"Two portions of skin showing parts of three small subcorneal vesicles in various stages of development. The vesicles contain very numerous polymorphs and one of them a portion of hair. Similar cells and many small hæmorrhages are present in the underlying dermis. Gram's stain shows degenerate Gram-positive staphylococci, mostly intracellular, in and just beneath the epithelium forming the floor of the vesicle. The most recent vesicle is centred round and communicates with a hair follicle."

Cultures from vesicles repeatedly negative.

Bacteriology (Dr. Mary Barber).—16.5.50: Material from the lesions produced *Staph. albus* only, though the skin of the wrist gave a culture of *Staph. pyogenes* as well. *Staph. aureus* was found in the nose.

6.6.50: Swab from the skin of the thigh showed *Staph. pyogenes* at intervals up to 30 minutes: after cleaning with spirit, *B. subtilis* and *Staph. albus* only were recovered except that after ten minutes broth culture revealed coagulase-positive staphylococci.

Treatment.—The following forms of treatment have had no effect on the condition:

Penicillin in full dosage—liq. arsenicalis—calciferol—various sulphonamides—local antiseptics as lotions, powders and pastes—ultraviolet light.

Sulphapyridine alone of these produces some degree of improvement, but this is not sustained. It is of interest that the "rheumatism" also benefits.

II. Mrs. M. M., aged 71. Housewife. Nearly three years ago this patient began to suffer from a pustular eruption, beginning on the neck and spreading to the axillæ, mammary regions and groins, where it has remained predominantly since. When she was first seen in 1948 the appearance was that of superficial pustules and shallow erosions, more or less grouped in these areas. The eruption appeared suddenly, but has spread gradually, and, during the last year, this has been markedly centripetal. She was in good health at the time of onset, and has had no previous illnesses of importance.

There is some itching when the patient is warm, but this is never intense.

Present appearance.—This patient looks healthy for her age. All the main folds of the trunk, and the proximal parts of the limbs, are the site of an eruption which has the appearance of spreading outwards, lesion by lesion. The individual element is a small vesico-pustule which rarely attains a diameter larger than 8 mm. It is surrounded by a pink areola and, in the course of a week, passes through the stages of enlarging, becoming scabbed, and leaving a thin, dry, yellowish flake on the skin. This drops off to leave a discoloured macule, but no pigmentation. The intervening areas of skin are normal, but evidence of previous pustules can be seen. In the last two weeks, confluence of lesions has taken place under the breasts.

Investigations.—General examination has shown no evidence of any marked abnormality. No toxic focus can be demonstrated.

Hb (1948) 90%; W.B.C. 21.5.48, 8,000; 11.11.49, 7,000; 15.9.50, 8,000. Normal differential counts.

W.R. and Kahn tests negative.

Nasal swab sterile.

Biopsy, July 1950.—

From axilla: (1) A small subcorneal cavity containing polymorphs. The lesion is centred round a hair follicle with the lumen of which it appears to communicate. The corresponding sebaceous gland has been destroyed and its site is now marked by a foreign body giant-cell reaction, the cells of which contain much lipoid material.

(2) A crust overlies a hair follicle whose epithelium is slightly hyperplastic and surrounded by a slight chronic inflammatory reaction. Adjacent is another hair follicle, atrophic and surrounded by scar tissue. This seems to be a folliculitis rather than an impetigo.

From chest wall: A small subcorneal bulla into which a few polymorphs are migrating through the epidermis. The superficial dermis beneath the lesion is slightly œdematous, contains a few polymorphs and one or two small hæmorrhages. (Dr. I. W. Whimster.)

After biopsy.—Culture from pustule: *Staph. albus.*

Bacteriology (Dr. Mary Barber).—8.8.50: *Staph. pyogenes* not isolated from any swab. Pustule showed *Staph. albus* as did the affected and unaffected area of the skin.

Treatment.—Many local antiseptics and dyes—liq. arsenicalis—penicillin—sulphonamides—have not materially affected the eruption, though sulphapyridine causes some temporary amelioration.

Dr. I. W. Whimster: I have three sections to demonstrate, one from each of Dr. Wilkinson's cases and one from Dr. Sneddon's case which he will describe. There is a striking similarity between them all; indeed it would be difficult to tell one from another.

The lesions consist of little blisters, the roofs of which are formed of horn and the floors of the remainder of the epithelium, the lumina containing a small amount of pus. The underlying dermis in all the cases is œdematous and infiltrated by polymorphs which can be seen migrating into the lumen of the vesicles. Two of the vesicles overlie and their lumina communicate with hair follicles and beneath the third there is a regenerating, partly destroyed follicle. Gram-positive cocci, often inside polymorphs, are present in the dermal papillæ of Dr. Wilkinson's second case but are not demonstrable in the lumen of the vesicle. The other two cases have not yet been examined histologically for the presence of organisms.

Dr. I. B. Sneddon: When I showed my case at the International Conference of Physicians in 1947 to many Continental dermatologists as well as to the people here the same difficulty in diagnosis arose. There seemed to be no clear opinion as to what the diagnosis should be. I think, however, having seen Dr. Wilkinson's cases, that there is no doubt that the case I showed was of the same group; there are minor differences but not significant ones.

It is difficult to believe that this is an infective condition since it goes on for so many years and no chemotherapy of any kind has produced more than slight temporary improvement in the cases; even more so since I have heard from Dr. Savage who is now looking after the case I showed, that he has been able to clear up the lesions by painting the skin with Thorium X. It is much more likely that it is a weird variation of a parapsoriasis which is appearing in pustular form.

Pustular Herpetiform Parapsoriasis.—JOHN SAVAGE, M.D.

The patient is now aged 59 and she has been under care now for about three years (Fig. 1). The eruption started in July 1945 with a pustule on the right buttock. Lesions next appeared on the arms, and in August the condition became very widespread, covering the front and back of chest, arms and upper thighs. The pustules come out in crops and eventually dry with a light crust. There has never been any irritation and during an acute relapse the patient feels well. She has never had a temperature or rigor. She has no idea what brings on

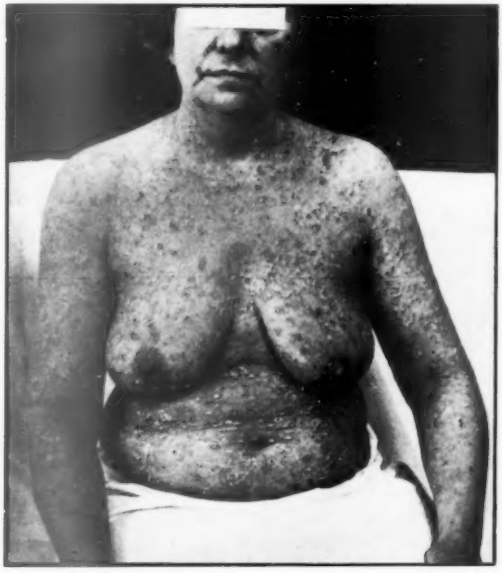

FIG. 1.—Mrs. C. Pustular herpetiform parapsoriasis. (Photograph 24.7.48.)

an attack but rarely a month passes without fresh lesions appearing. She takes no regular medicines. The face has never been affected, the eruption being limited to the bathing costume, pityriasis rosea, distribution. The hair and nails are normal. The mucosa of the mouth has never been affected and her general health has been perfect. Periods stopped aged 44. There is nothing of note in the previous or family history; she has had two daughters and one son, and during the pregnancies she had no skin eruptions.

The lesions always begin with pustules, no vesicles or papules have ever been seen. The pustules dry with a light flat crust which peels off like candle grease. Lesions are widely scattered and show herpetiform grouping. The surrounding skin is dull-red in colour with no infiltration. The lesions heal without scarring. The palms, legs, feet, face and scalp have never been affected.

All special investigations have shown no abnormality. No relapse when iodides were given by mouth.

The patient had intensive treatment with penicillin, the sulphonamides (including sulphapyridine), calciferol, anti-histamine drugs and repeated vaccination. Neither the course nor the relapse rate was affected. Local U.V.R. helped by drying the pustules more quickly but did not prevent relapses. Fractional X-ray therapy had no effect, but it is very interesting to see the effect of Thorium X. The strength used was 3,000 units per c.c. of acetone varnish base. Paintings were started on the right side of back on October 3, 1949, using approximately 2–3 c.c. at a time and the photograph (Fig. 2) was taken on November 24, 1949. The area treated with Thorium looks much the same to-day. She has had many severe relapses but the Thorium-treated areas have remained clear.

FIG. 2.—Effects of painting right side of back with Thorium X.

The diagnosis of impetigo herpetiformis was made when this patient was shown at the Dermatological Section of the International Conference of Physicians in London, 1947.

This condition was described by Hebra in 1872. He described 5 cases, all of them in pregnant women, 4 of whom died under observation, the fifth died during a relapse in a subsequent pregnancy. In his description of the cases Hebra stressed eight characteristics which later became known as "Hebra's postulates".

By 1887 Kaposi had collected 13 cases, all of whom died. One patient was a male.

Since this time cases have been reported as occurring in virgins, non-pregnant women, climacteric women, men and boys and to Hebra's postulates have been added other characteristics (Hall, 1944).

Anderson (1944) considers that apart from the cases described by Hebra there is another group with sufficient distinguishing features to permit one to place them in a separate group.

I consider that the name impetigo herpetiformis should be reserved for the type of case described by Hebra and that some of the other cases, including this one, would best be classified in the parapsoriasis group. The following tables show, on the left, the similar and on the right, the dissimilar characteristics which this case has with both impetigo herpetiformis and the parapsoriasis group.

TABLE I.—IMPETIGO HERPETIFORMIS

(1) Pustules are filled with pus from their first appearance	Patient is otherwise healthy. Severe attacks are never preceded by fever or rigors
(2) Vesicles or circle of vesicles are never present	Post-menopausal
(3) Pustules are arranged in groups or rings which by drying turn into yellow, flat crusts underneath which the skin is red and moist	No hypocalcæmia
(4) Involved areas heal with an unusual reddish-brown pigmentation	
(5) Contents of pustules are sterile	

TABLE II.—PARAPSORIASIS

(1) Patient is otherwise healthy	No cases have been reported where the lesions are pustular from their first appearance and show herpetiform grouping
(2) The dermatosis is chronic and subject to spontaneous exacerbations and remissions	
(3) No subjective symptoms. No itch	
(4) No distinctive histology	
(5) The distribution is similar to that found commonly in guttate parapsoriasis	
(6) When the pustules dry, although more yellow, they peel off exactly like a guttate parapsoriasis and the scaly lesions of pityriasis lichenoides chronica	
(7) Many lesions of parapsoriasis clear or are greatly improved by treatment with Thorium X whereas they are unaffected by X-ray therapy	

To quote Colcott Fox and MacLeod (1901) when they described a case of parakeratosis variegata, "This case presents such definite clinical peculiarities of its own, distinguishing it from the other members of the group although associating them together that it deserves a more specific title". The same may be said of the case described above. The name I suggest is pustular herpetiform parapsoriasis.

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Dr. J. Sommerville: How long was it before results began to appear in the painted area?

Dr. J. Savage: The dramatic effect was seen when she had her next relapse. The treated area was clear and remained clear during subsequent relapses.

Dr. D. I. Williams: Have you painted any areas just with the varnish alone?

Dr. Savage: No.

Dr. A. Lyell: I have been impressed by the history of drug-taking in the first of Dr. Wilkinson's cases. The lady with the more generalized eruption has apparently taken a proprietary purgative which contains phenolphthalein for longer than she has had the eruption. Every time she takes it the eruption gets worse, it lasts for a few days and then settles down to its more normal state. She has been taken off these tablets for some length of time but one of the characteristics of phenolphthalein eruptions is their persistence.

Dr. J. Sommerville: I think the term "impetigo" is unfortunate; it is a pity to classify these eruptions as—what is a fairly well-recognized condition—impetigo herpetiformis. I cannot see that they could be put into that group. I am glad to hear the remarks about Dr. Wilkinson's first case; I thought the second case somewhat resembled the case which has been so excellently presented by Dr. Savage.

For treatment of these I would have suggested generalized light therapy and I am very glad to learn that something akin to it has been used, and with response, namely—Thorium X.

Dr. A. C. Roxburgh: How long did the effect of Thorium X continue? In other words, how long was it after the painting with Thorium X before a relapse occurred which was prevented on the painted area?

Dr. P. J. Feeny: I am doing some work on parapsoriasis with Thorium X. I think the guttate variety is completely resistant to Thorium X but parapsoriasis *en plaque* does respond temporarily. It is supposed to be a premycotic infection, which should be of additional interest to Dr. Savage in this case.

Dr. E. Lipman Cohen: I think it would be worth while investigating the possibility that a virus is causing this condition.

Dr. Savage (in reply to Dr. Roxburgh): The effect of the Thorium X on this area of the back has continued to the present. In the first instance she had a severe relapse six weeks after the paintings were started, relapse was prevented on the painted area and that is when the photograph (Fig. 2) was taken.

Dr. Wilkinson (in reply, 6.3.51): Thorium X has been used on both cases at intervals of two and three weeks. The immediate result was very satisfactory and Mrs. M. M. has stayed fairly clear of lesions up to the present. Mrs. E. L., however, has relapsed after an initial improvement and the lesions are now widespread on both treated and untreated areas. Varnish alone, used as a control, did not alter the eruption. This patient, incidentally, has taken no phenolphthalein now for over six months. Generalized ultraviolet light had been used previously without success.

The following cases were also shown:

Recurrent Leg Ulceration.—Dr. F. RAY BETTLEY.

(1) **Circinate Lichen Planus.** (2) **Lupus Vulgaris.**—Dr. F. SHERRY-DOTTRIDGE.

Familial Benign Chronic Pemphigus.—Dr. E. WADDINGTON.

Necrobiosis Lipoidica Diabeticorum.—Dr. CLARA M. WARREN.

Leiomyoma Cutis.—Dr. I. S. HODGSON-JONES (for Dr. R. M. B. MACKENNA).

Lichenoid Gold Eruption.—Dr. R. J. CAIRNS (for Dr. G. B. MITCHELL-HEGGS).

(These cases may be published later in the *British Journal of Dermatology*.)

Section of Orthopædics

President—A. T. FRIPP, M.B.Oxon., F.R.C.S.

[*October* 3, 1950]

Chondroma of Femur with Sarcomatous Changes.—R. C. F. CATTERALL, M.Ch., F.R.C.S.

The patient, Mrs. A. B., aged 64, who had been treated July 1948 for hypertension and obesity, fell down in September 1948 and sustained a fracture of the upper third of the left femur (Fig. 1). This was reduced and immobilized in extension, but it was almost a year before union was sufficiently advanced to allow weight-bearing (Fig. 2). Ten months later she was readmitted to hospital following another fall, and an X-ray (Fig. 3) showed

FIG. 1.—Original fracture through ? weakened area of femur.

FIG. 2.—Union of fracture one year later.

FIG. 3.—Pathological re-fracture two years after the original fracture.

extensive bone changes throughout the upper third of the femur with a pathological fracture through the base of the neck. All the blood-chemical investigations were within normal limits, a biopsy showed increase in marrow fibrosis only. The clinical progress since readmission has been that of slow progress of the clinically malignant mass in the thigh.

Review of the original injury suggests that this fracture was also pathological and there is little doubt that this is a case of chondroma of the femur becoming sarcomatous after repeated injuries.

Polyarthritis with Unusual Bone Changes.—W. WAUGH, F.R.C.S. (for ST. J. D. BUXTON, F.R.C.S.).

J. P. W., male, aged 65.

History.—May 1945: First seen complaining of pain and swelling in the right knee which had been present for eighteen months. A diagnosis of senile tuberculous arthritis was made.

July 1945: Excision and arthrodesis of the right knee. Microscopy of material obtained at operation showed non-specific inflammatory changes in the synovial membrane, erosion of articular cartilage, widening of haversian canals and increase of fibrous tissue. There was no evidence of tuberculosis.

November 1945: Solid bony ankylosis of the right knee had been obtained.

January 1946: Pain and swelling developed in the left ankle. The clinical picture was of a subacute arthritis and X-rays showed no abnormality. The ankle was immobilized in plaster of Paris.

May 1946: Although the symptoms in the left ankle were much improved, X-rays now showed narrowing of joint space and some sclerosis in the talus and navicular (Fig. 1). In the X-rays of his skeleton which were taken at this time there was no other abnormality.

December 1946: There was no pain in the left ankle and right knee (ankylosed) but he complained of pain and stiffness in both wrists and elbows. X-rays of the left ankle showed that erosion of cartilage and bone with dense sclerosis of the lower end of tibia, talus, os calcis and navicular had developed. At the same time similar changes, but of less severity, were beginning in both wrists and elbows.

Present condition.—He complains of severe pain in both wrists and elbows. There are no other symptoms and his general health is good.

Examination shows limitation of movement and crepitus of both elbow-joints. There is peri-articular thickening of both wrists, with limitation of movement of the right and full movement of the left wrist. There is solid ankylosis of the right knee. Movements of the left ankle are good, but there is considerable peri-articular thickening. All other joints are normal. There are numerous small subcutaneous lumps on the arms which are presumably neurofibromata. There is no abnormality of the central nervous system.

FIG. 1.—Left ankle, May 1946.

FIG. 2.—Left ankle, March 1950

FIG. 3.—Right wrist, March 1950.

FIG. 5.—Left foot, September 1950.

FIG. 4.—Right elbow, September 1950.

X-rays.—The joints affected are both wrists and elbows and the left ankle. These show erosion of cartilage and destruction of bone which is not confined to articular surfaces. The neighbouring bones show a very dense sclerosis, the extent and degree of which is well illustrated in Figs. 2, 3, 4 and 5. The remainder of the skeleton is normal, apart from a dorsal scoliosis and some intervertebral lipping.

Investigations.—Blood count: A mild hypochromic anæmia was found in March 1950 and this improved rapidly with iron. Apart from anisocytosis and poikilocytosis, no abnormal red cells were seen. The white cell count has always been within normal limits.

Blood sedimentation rate is at present 12 mm. in the first hour (Wintrobe corrected). During 1945 to 1948 it has varied from 29 to 59 mm. in the first hour (uncorrected).

Wassermann reaction and gonococcal complement-fixation test were both negative (in 1947 and 1950).

Serum phosphorus, calcium, alkaline and acid phosphatase have been repeated on several occasions and have always been within normal limits.

Comment.—The clinical picture is of a chronic, and, at present, inactive arthritis involving both elbows and wrists, and the left ankle. The feature of interest is the X-ray appearances. A gonococcal arthritis or a secondary deposit from a carcinoma of the prostate has been excluded as far as possible, and there is no evidence to suggest any obscure form of industrial poisoning. It is unlikely that the dense sclerosis might represent a primary bone lesion since the history shows that in the left ankle, for example, a subacute arthritis without X-ray changes was the first stage, and that the erosion and sclerosis developed subsequently and progressed as the joint condition became less active clinically. This suggests that the basic lesion is an infective arthritis of unknown origin which is associated with unusual changes in the neighbouring bones.

Pre-pseudarthrosis of Tibia with Presumed Neurofibromatosis.—J. H. MAYER, T.D., M.B., F.R.C.S.

S. M., male infant, aged 16 months.

Angular bowing of lower tibia and fibula shafts noted since birth and tending to increase.

FIG. 1. FIG. 2.

FIG. 1.—Radiograph at 4 months. Bowing of tibia and fibula, with cystic changes in tibial shaft.

FIG. 2.—Radiograph at 16 months. Bowing slightly diminished, cystic changes still present though less pronounced. Slight subperiosteal new bone formation in concavity of tibia.

X-rays show cystic changes in affected part of the tibia (Fig. 1). Some attempt at new bone formation in the concavity of the tibia in more recent films (Fig. 2). No evidence of fracture.

Child also has patches of *café-au-lait* skin pigmentation. Mother has similar patches and also subcutaneous neurofibromatous nodules. Sister also has *café-au-lait* patches.

Blood chemistry showed evidence of mild rickets now returning to normal on treatment.

It appears probable that this case will terminate in pseudarthrosis of the tibia. Recent reports especially from America emphasize the close relationship of pseudarthrosis with neurofibromatosis and this case appears to belong to the class. Because of the probability of pseudarthrosis ensuing the leg has been kept on a padded metal splint since first seen at the age of 4 months.

In discussion it was suggested that no external splint would be likely to prevent pseudarthrosis and if worn it would have to continue in use until the age of about 14 years. The encouraging results of dual grafting in pseudarthrosis were also mentioned.

Hypertrophic Arthritis with Neurological Lesion.—J. H. MAYER, T.D., M.B., F.R.C.S.

G. C. P., male, aged 45.

Eleven years' history of gradually increasing stiffness and deformities of wrists, hands and feet with pain, also gradual appearance and enlargement of subcutaneous tumours on both forearms and hands.

Examination and X-rays (Figs. 1, 2 and 3) show hypertrophic degenerative arthritis of inferior radio-ulnar, carpal and tarsal joints, and degenerative changes in finger and toe joints suggestive of gout; dorsal subluxation of both ulnar heads. There are also signs of mild spastic paraplegia with extensor plantar responses and exaggerated knee and ankle jerks, and absent biceps and supinator jerks on the left.

C.S.F., blood counts and blood chemistry all normal. W.R. and Kahn and gonococcal C.F.T. all negative.

Biopsy of tumours from right forearm and hand show appearance of a chronic rheumatic lesion.

FIG. 1.—Radiograph of right and left hands and wrists, showing multiple joint changes.

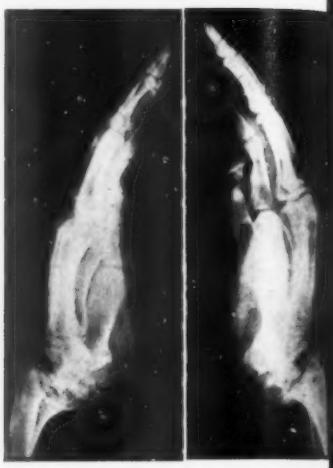

FIG. 2.—Lateral views of right and le hands and wrists: dorsal subluxation ulnar heads.

FIG. 3.—Radiograph of right and left feet, showing changes in tarsal joints and toe joints.

A neurologist had failed to make a diagnosis of the neurological condition but stated that this was not syringomyelia. It seemed impossible to account for the joint changes, subcutaneous tumours and paraplegia on a single pathology, and there were no fresh suggestions from the Meeting.

Unilateral Condylar Hypertrophy (Mandible).—PATRICK CLARKSON, F.R.C.S., and Professor MARTIN RUSHTON, M.D.

This case of a not uncommon condition is shown because of the difficulties presented in diagnosis.

Male, aged 19.

History.—Six weeks ago "he felt his jaw go". He then for the first time noticed the cross bite and the pain and tenderness over the right temporo-mandibular joint. At hospital a diagnosis of "Dislocation of the Right Temporo-Mandibular Joint" was made. He was twice manipulated under pentothal anæsthesia. He states that manipulations gave him "temporary relief only". He subsequently reported to a Dental Department where the clinical diagnosis of "Temporo-Mandibular Dislocation" was made again. Two further manipulations under general anæsthesia were done without relief.

FIG. 1A.

FIG. 3.

FIG. 4A.

FIG. 1B.

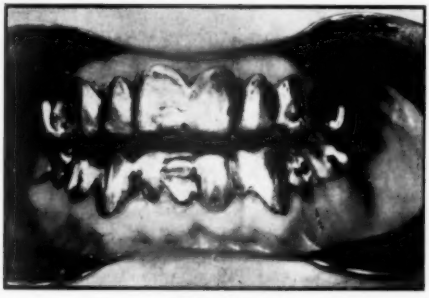

FIG. 4B.

FIG. 2A.

FIG. 2B.

FIG. 1, A and B.—The pre-operative view showing the asymmetry of the face and the cross bite.

FIG. 2, A and B.—Pre-operative X-rays. A, The lateral view shows that the right condylar head is considerably larger than the left and that the right glenoid fossa has been enlarged. B, The A.P. view shows that most of the right mandible has to some extent shared in this enlargement. The coronoid is not affected.

FIG. 3.—Operative specimen. The condylar head is enlarged and greatly flattened and shows the osteophytic formation.

FIG. 4, A and B.—Post-operative photograph. A week after operation. The jaws were fixed in cast metal splints for one week. He wore a flange on the lower splint for six weeks.

When seen by M.R. it was possible to demonstrate clinically and by X-ray that both condylar heads were in the correct anatomical position in the glenoid fossæ, and that the right condylar head and the whole right mandible were enlarged in all dimensions compared to the left, causing deviation of the chin to the left, cross bite, and early prognathism.

This condition of unilateral condylar hypertrophy is one of which an increasing number of cases have been reported in recent years. The usual presenting symptoms are the facial asymmetry and the progressive malocclusion. A history of trauma without fracture is not uncommon. The arthritis and the distortion of the capsule produced by the enlarging head can cause acute arthritic episodes which lead some patients to seek medical aid.

Treatment.—Treatment in relatively mild cases, like the present one, is by a radical condylectomy. When the prognathism and the asymmetry are more marked the condylectomy on the affected side may have to be combined with an osteotomy of the ascending ramus on the non-affected side to obtain the best possible reduction and occlusion. Resections of the horizontal ramus in the symphysis region are sometimes needed to restore facial symmetry.

On 24.10.50 a radical condylectomy was done, through a one inch infero-lateral approach and using a Kostecka condylar needle for insertion of the Gigli saw by which the neck was divided.

Forequarter Amputation for Sarcomatous Degeneration in Paget's Disease in the Humerus with Lymphatic Spread.—F. G. St. Clair Strange, F.R.C.S.

Case report.—Miss A., aged 59, a laundry supervisor, was first seen on May 9, 1950. Her history was that in 1946 she had had a fracture of the lower end of the right humerus (Fig. 1) and union had resulted after rather prolonged treatment. In January 1950 there was gradual onset of pain and limitation of movement in the right shoulder, and a swelling of the shoulder had recently become apparent.

On examination her general condition was good: she lacked obvious stigmata of Paget's disease, and presented a diffuse swelling around the anterior and lateral aspects of the head and upper shaft of the right humerus, with marked restriction in shoulder movement. The swelling was firm and fixed, but not tender.

Fig. 1.—X-ray of 18.10.46, showing pathological fracture of R. humerus in typical Paget's disease.

Fig. 2A.—X-ray of 18.6.50. Osteogenic new growth in the head and upper shaft of the same bone.

Fig. 7.—The humerus sectioned, showing new growth in upper end, but also largely replacing upper half of shaft. Two or three discrete areas of tumour in lower end of shaft.

The X-ray (Fig. 2A) showed the appearance of Paget's disease of the humerus with an osteogenic new growth arising from the lateral aspect of the head and upper shaft. The only other evidence of Paget's disease was some increased density of the cortices of the femora over a short area in their upper one-thirds.

A diagnosis of osteogenic sarcoma arising in Paget's disease of the humerus was made and the patient admitted to the Kent and Canterbury Hospital. Biopsy was performed on 19.5.50 and Dr. I. B. Morris reported that it showed a moderately well-differentiated osteogenic sarcoma (Figs. 3, 4). The diagnosis of Paget's disease is confirmed by the microscopic appearance of the bone (Fig. 2B).

While the wound was healing 2,000 r deep X-ray treatment spread over twelve days was given and on June 2, 1950, forequarter amputation was performed. Two days later the patient started getting up and on the twelfth day primary healing was observed at the time of removal of the stitches. A light hollow plaster of Paris prosthesis was made to give a

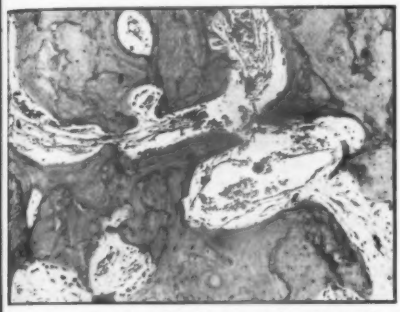

FIG. 2B.—Section of R. humerus showing typical Paget's disease. Mosaic well shown and also fibrous replacement. (Right low centre.) × 25.

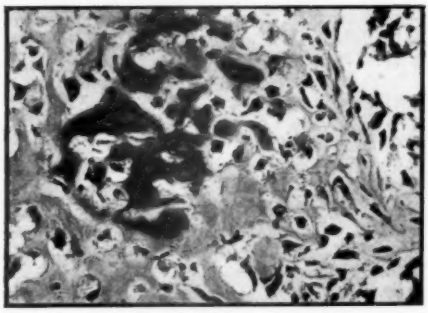

FIG. 3.—Bone formation in sarcomatous area of humerus. × 200.

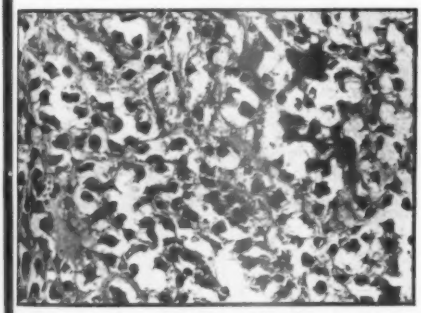

FIG. 4.—A less well-differentiated zone, though even here an attempt is seen at the laying down of an intercellular stroma. × 200.

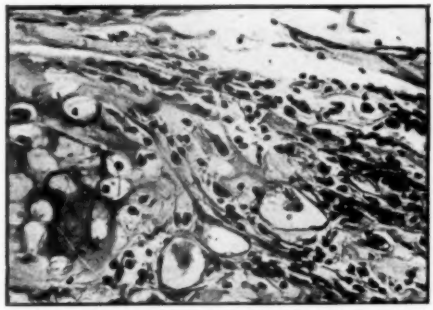

FIG. 6.—High-power view of centre of same field as Fig. 5. Lymph gland being invaded by osteogenic new growth. × 200.

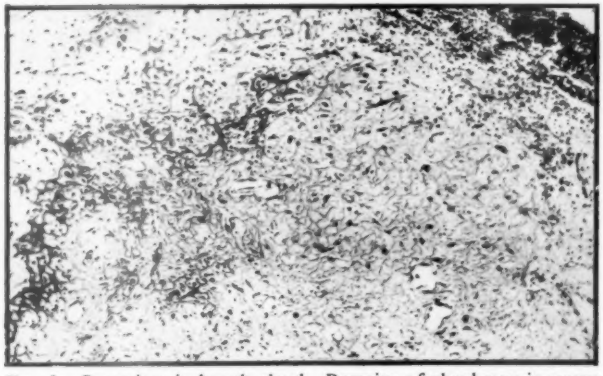

FIG. 5.—Secondary in lymph gland. Remains of gland seen in upper right corner. Some osteogenesis in new growth to left. × 32.

shoulder to enable her to wear her clothes and she was discharged on the fifteenth day. She returned to her employment on the seventeenth post-operative day.

The interesting point about this case was that, during the course of operation, a hard swelling was found low in the axilla and rather close to the chest wall, which on section proved to be a bone-forming metastasis in a lymphatic gland (Figs. 5, 6). In addition, in the lower end of the humerus there were two or three discrete tumours apparently arising separately from the main one (Fig. 7).

(The patient died of pulmonary and superior mediastinal spread just six months after amputation.)

Discussion.—Metastasis to lymphatic glands in bone sarcoma is rare. I have, however, since seen the case records of a late patient of Mr. F. W. Holdsworth of Sheffield, in which there was extensive lymphatic and retroperitoneal spread from a sarcoma arising in Paget's disease in the os calcis.

References in the literature are rare, and Willis (1934 and 1948) refers to 8 undoubted cases of osteogenic sarcoma spreading to lymph nodes and adds 3 of his own. He quotes Warren and Meyer (1938) who found in 237 non-lymphoid sarcomas, 12 cases of fibrosarcoma and 8 other cases (including osteosarcoma, leiomyosarcoma and rhabdomyosarcoma) in which lymph nodal spread was noted. I have personally also seen a case of massive lymph node and pulmonary and heart muscle secondaries in a fibrosarcoma of upper thigh in an infant of 6 months. Of all these, only one case, that of Albertini's (1928), was in a case of Paget's disease, so that it would appear that Albertini's, Holdsworth's and the present cases are the only ones so far discoverable in whch sarcoma in Paget's disease has spread to the lymph glands. (Two of Bird's cases are very suggestive, though unproven, and not accepted therefore by Willis.) Platt's (1947) 10 cases did not demonstrate this finding, which was not recorded either by Davie and Cooke (1937) or Fairbank (1950). Davie and Cooke, indeed, in their thorough review, fail even to mention the possibility of its occurrence. Willis (loc. cit.) refers to two instances of bone sarcoma in dogs spreading to lymph glands.

Spread to the pleura is, of course, recognized, as is the multiplicity of primary tumours in bones affected by Paget's disease.

Summary.—A case of osteogenic sarcoma arising in a humerus the site of Paget's disease, is demonstrated, treated by forequarter amputation after irradiation. Multiple primaries were present in the humerus and a bone-forming secondary was found in an axillary lymphatic gland. This is only the third undoubted case of this occurrence in "Paget's sarcoma", that I have been able to find.

I am greatly indebted to Dr. L. W. Proger of the Pathological Department of the Royal College of Surgeons for preparing and mounting the specimen and Dr. H. D. Ross of the same department for the micrographs and photograph of the specimen.

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Old Tuberculosis of Left Hip Ankylosed in Abduction, Short Left Leg, Partial Peroneal Palsy.—O. J. VAUGHAN-JACKSON, F.R.C.S.

D. V., male, aged 18.

In 1941 tuberculosis left hip and knee. Nursed in a frame. After two and a half years' recumbency, it was noted that when he got up he had lost some power in his left foot. 1947: sustained a fracture upper and left femur. Treated in a plaster spica. After this was removed he had 5 cm. of apparent shortening of the left leg, which was corrected by a raised boot. For one year progressive inversion of the left foot with resulting instability and untrustworthiness of the leg. He falls fairly frequently and he is liable to strain and hurt the left knee.

On examination.—Left lumbar, right dorsal scoliosis. Scars of old pressure sores and sinuses right buttock. Left hip ankylosed in 30 degrees abduction, 10 degrees flexion. 12·5 cm. true shortening, 5 cm. apparent shortening of the left leg (Figs. 1 and 5). Left knee shows lateral instability and a restricted range of 185–125 degrees (Figs. 2 and 3). Left foot inversion deformity not fully correctable (Fig. 4), with restriction of subtaloid and mid-tarsal movements. Marked weakness of extensor hallucis longus and extensor digitorum longus and peronei. No sensory loss.

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 1.—Radiograph showing ankylosis in wide abduction.
FIGS. 2 and 3.—Radiographs showing marked arthritic changes in left knee.
FIG. 4.—Radiograph showing early arthritic changes in the left ankle.
FIG. 5.—Showing the flexion abduction deformity of the hip and varus deformity of the foot.

Mr. Vaughan-Jackson in discussion said: It seemed fairly clear that in order to stabilize this patient and deal with his complaint of falling over and wrenching his foot, he would probably need that foot stabilizing in a correct position. Supposing that were agreed upon, the discussion at the hospital a few days previously centred around what else if anything should be done. Should there be any correction of the abduction-flexion deformity of the hip? In view of the 12·5 cm. true shortening, some abduction seemed to be desirable. But this must cause, in the long run, considerable strain on the opposite hip, predisposing to a degenerative arthritis; in addition there would be strain on the low back. Could a case be made out for correcting the alignment of the bad hip by some form of osteotomy, and, accepting the increase of shortening, giving him a higher and perhaps a heavier boot? That was, very briefly, the problem.

Mr. R. C. F. Catterall said that this case showed a grossly short leg with a stiff hip, a bad ankle and an unstable knee. Amputation through the upper thigh, although a desperate remedy, should surely be seriously considered under the circumstances.

Mr. Vaughan-Jackson said that there were possibilities along the line that Mr. Catterall had suggested. He had had occasion to ask Mr. Buxton's opinion in another case where the hip was fixed. Personally he himself had had no experience of fitting limbs on to arthrodesed femoral stumps, but Mr. Buxton had told him the prognosis was quite good.

In reply to a member who said that the X-ray picture showed on the left hip a very firm ankylosis, and questioned whether, with the condition of the knee, it was really a true old tuberculosis, Mr. Vaughan-Jackson said that on that point he had no positively accurate information.

Judet's Operation for Aseptic Necrosis of Head of Femur.—K. I. NISSEN, F.R.C.S.

History.—Mrs. F. G., aged 64, sustained a subcapital fracture of the left femur in April 1948. A Smith-Petersen pin was inserted in good position. Eighteen months later pain commenced

in the hip and thigh, and steadily increased. Radiographs taken in August 1950 showed aseptic necrosis with collapse of the head and protrusion of the pin into the joint (Fig. 1).

Operation (3.8.50).—The Pidcock pin and the nail were extracted through a short transverse lateral incision. By way of the anterior approach to the hip-joint, the rectus femoris was reflected downwards, the anterior half of the capsule was excised and the whole of the necrotic head was removed. As the track of the Smith-Petersen pin was not quite central in the neck a fresh channel for the stem of the Judet's prosthesis was drilled alongside it down to the lateral cortex, which was perforated with a ¼ in. osteotome. The selected prosthesis had a stem of 8 cm. and a head 45 mm. in diameter. The neck was carefully trimmed to fit into the mushroom head before final impaction with a concave punch made of soft wood (Figs. 2A and 2B).

After-treatment.—Light skeletal traction with a tibial pin, Tulloch-Brown's U-loop, and full control of external rotation, was maintained for three weeks. Flexion and extension, abduction and adduction were encouraged after four days. The traction was changed to skin traction for the fourth week. The fifth week was spent mostly in an armchair. By this time the patient could raise the leg straight to 50 degrees with ease, and the range of passive flexion was 65 degrees.

FIG. 1.

FIG. 2A.

FIG. 2B.

At two months.—Active straight leg raising 60 degrees; passive flexion 0–90 degrees; abduction 20 degrees; adduction 15 degrees; external rotation 20 degrees; internal rotation 10 degrees.

There is no measurable shortening. The patient is completely free from pain, walks at good speed with one stick and a full stride, and can manage stairs.

POSTSCRIPT.—At three months she discarded the stick indoors and ceased treatment at her own request.

Mr. Nissen said that the early return of muscular control of the hip was a feature of the Judet's procedure. In another patient with aseptic necrosis who had been bed-ridden for six months the shaft of the decalcified femur fractured on attempted dislocation of the hip. This could probably have been avoided by subcapital section of the neck in situ and removal of the necrotic and adherent head piecemeal. The fracture united uneventfully with simple traction, and at three months the patient was walking well with crutches, free from pain.

The Judet's operation might prove to be the procedure of choice for cases of aseptic necrosis with a good acetabulum but a disorganized femoral head.

Mr. O. J. Vaughan-Jackson said that there was no question but that the result they had seen that evening was excellent, but he could not help feeling a little worried as to whether the prosthesis would loosen in time. Even given that the substance was absolutely inert and the whole thing was an adequate carpentering fit, and the strains of weight-bearing were in the vertical plane, he was astonished that more of Judet's cases had not come loose. Any hard inert body like this, one felt, was likely to loosen as time went on.

Mr. W. A. Law said that he had not been unduly impressed with the results of the procedure in osteo-arthritis, but for the sort of case now shown it was certainly a procedure worthy of consideration. It involved a more simple operation. One was not faced with the reconstruction of the acetabulum as one was in many cases of osteo-arthritis. He thought that with the avascular head of the un-united fracture of the head of the femur this operation was worth a prolonged trial. One would just have to wait to find out what happened in the course of ten or fifteen years. He said that many continental surgeons did nothing to the acetabulum. There was a large marginal ring of bone posteriorly which must act as a block, but they do not reconstruct the acetabulum in the manner of the arthroplasty operation.

Section of Epidemiology and State Medicine

President—W. H. BRADLEY, D.M., M.R.C.P.

[*October* 20, 1950]

The Character and Distribution of Disease in American Industries Using Beryllium Compounds

By HARRIET L. HARDY, M.D.

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THE great increase in the use of beryllium compounds in the last fifteen years in the United States has resulted in the appearance of variable syndromes having, as I hope to prove, a basic pattern. For reasons of clarity, I shall speak of the pathological effect of incriminated beryllium exposures as beryllium poisoning, modifying this title as needed to indicate clinical syndromes.

Within limits depending more on the quantitative than the qualitative beryllium exposure, the worker may suffer an acute, subacute or chronic form of the disease.

Acute.—Gross exposure produces in a fairly high number of non-protected workers contact dermatitis, conjunctivitis, upper respiratory tract irritation and, in a smaller number, bronchitis and pneumonitis. If the lower respiratory tract is involved, weight loss, cyanosis, dyspnœa, drop in vital capacity are abruptly noted. Treatment consists of complete bed rest, administration of adequate amounts of oxygen and prolonged convalescence up to four and six months. Before the seriousness of beryllium pneumonia was recognised several patients died as a result of return of pulmonary œdema consequent on early ambulation (Van Ordstrand, Hughes, De Nardi and Carmody, 1945). Treated with rest, the pathological changes shown on the chest X-ray clear up, demonstrating the complete reversal of acute beryllium pneumonia. This clearing may take six months or longer. Similar episodes but of a much milder X-ray and clinical character are noted, requiring, however, in some instances as long as a year for complete clearing (Aub and Grier, 1949).

Subacute.—An intermediate clinical syndrome of subacute illness is encountered in which there is a clear story of beryllium exposure. Beryllium can be detected in the urine (Cholak and Hubbard, 1948), the X-ray picture shows fine nodularities in both lung fields, but the patient, while losing weight and suffering mild dyspnœa and easy fatigue, is able to continue at some type of work.

Chronic.—Chronic beryllium poisoning has been designated because of outstanding pulmonary affections as delayed chemical pneumonitis. At the Saranac Symposium 1947 (Vorwald, 1950) it was designated "pulmonary granulomatosis of beryllium workers", a term which, in my opinion, is too narrow, as it refers to one histopathological phase and serves the clinician not at all.

In many cases, symptoms arise after apparently fantastically low-level exposures, varying in length of time from two weeks to several years of steady beryllium exposure and in a few instances after intermittent laboratory exposure. In analysing our data, we find that concurrently with fairly heavy exposure, a few non-protected fluorescent lamp manufacturing workers developed the chronic disease. In the majority of cases, however, a period of delay varying from a matter of a few months up to nine years has elapsed between cessation of beryllium exposure and onset of symptoms. Since we are discovering new cases, the possible period of delay is unknown. Very often a precipitating medical episode appears decisive—an infection, pregnancy or thyroid dysfunction. The patients uniformly complain of weight loss which may be profound.

Loss of weight, asthenia, dyspnœa on effort progressing to orthopnœa, cough and later bouts of gastro-intestinal disturbances are usual complaints. Punch biopsy of the liver (Fig. 1) confirms the existence of beryllium hepatitis, with pathological picture similar to that seen in autopsied cases, and beryllium present in the tissue. The lung involvement is bilateral, apex to base in distribution, causing hilar lymphadenopathy, sometimes to a remarkable degree; marked emphysematous changes and spontaneous pneumothorax may occur.

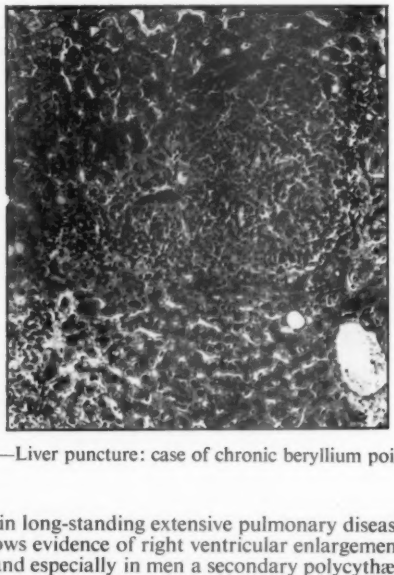

FIG. 1.—Liver puncture: case of chronic beryllium poisoning.

As might be expected in long-standing extensive pulmonary disease, the electrocardiogram in a number of cases shows evidence of right ventricular enlargement; the oxygen saturation of the blood is lowered and especially in men a secondary polycythæmia frequently develops. Skin tuberculin tests have been positive in about the same proportion as in the general population. Renal calculi have occurred in ambulatory as well as bed patients, in nearly one-fifth of the cases. Hypercalcæmia was a notable feature of metabolic studies done by Dr. William S. McCann's group at the Strong Memorial Hospital at Rochester. This group also found that patients with chronic beryllium disease are in negative nitrogen balance, which has considerable bearing on the great wasting in this disease. The 17-ketosteroid level in the urine is low as in many chronic illnesses and occasionally judicious use of testosterone has increased vigour and weight.

Death in chronic beryllium poisoning takes place in about 20% of the cases. Right-sided heart failure, cerebral anoxia, intercurrent respiratory infection and, in a few cases, overwhelming inanition and profound cachexia are recorded as terminal episodes.

Chronic beryllium poisoning is in most diagnosed cases a serious disease of long duration with a poor prognosis, going through periods of remission and exacerbation. The small but definite group who have severe bouts of hyperpyrexia make one wonder if the beryllium stored in the tissues has somehow become mobile to cause this reaction. A worker-patient only rarely returns to work, and those few who do have little endurance, complain of dyspnœa on effort or with slightest respiratory infections. The asymptomatic group contains at present, to my certain knowledge, a small number of workers—less than ten—with clear history of chronic exposure to beryllium compounds known to produce disease who have widespread chest X-ray changes in the lung fields and are excreting beryllium in the urine but are without complaints. The group characterized earlier as having what may be called subacute beryllium disease have signs and symptoms of beryllium poisoning but are able to do some work.

There is one important course that beryllium disease may take that should be emphasized. In a few cases, a worker may have one or more attacks of acute beryllium pneumonia, and after a variable period of time, with or without further beryllium exposure, may develop the chronic form of the disease. This may be a rare occurrence or may prove a serious source of chronic beryllium poisoning, since probably at least four hundred workers suffered the acute disease and doubtless many other cases were misdiagnosed as virus pneumonia.

At varying times in the clinical course of chronic beryllium intoxication, the total serum protein and globulin, liver function studies, urinary calcium, serum calcium and phosphorus, electrophoretic pattern of serum, alkaline phosphatase and urinary steroids have been reliably reported as abnormal in a varying number of cases. The interpretation of these abnormal findings is by no means certain at present. Liver function studies mentioned include bromsulfalein retention test (5 mg. per kg), cephalin flocculation test and the prothrombin time value. Where done, the punch biopsy may show hepatic pathology while liver function tests are normal. It is of interest that cephalin flocculation tests and electrophoretic patterns are abnormal in acute as well as chronic beryllium poisoning, with other findings, suggesting that these two clinical syndromes are different phases of a similar systemic reaction to a toxic insult.

There is much speculation as to the meaning of the disturbed levels—and they may be above or below normal—of serum calcium and phosphorus and alkaline phosphatase. Dr. Franklin McLean says that work in his laboratory points to direct intoxication of the process of calcification by beryllium rather than the development of beryllium rickets as previously reported. Work with beryllium[7], a radioactive isotope of the element made at the Berkeley cyclotron (Crowley *et al.*) shows that, in tracer experiments with small laboratory animals, beryllium goes into the bone and remains there (Wilson, 1948). It will be recalled that Dr. Leroy Gardner produced osteogenic sarcomas in rabbits with the beryllium compounds to which workers are exposed (Gardner and Heslington, 1946). No malignancies have appeared as yet among the human victims of beryllium poisoning. Grier *et al.* (1949), Klemperer *et al.* (1949) and DuBois *et al.* (1949), working independently, have satisfied themselves that beryllium *in vitro* and *in vivo* has an inhibitory effect on the alkaline phosphatase enzymes. Workers in Europe (Caccuri, 1940, and Aldridge, Barnes and Denz, 1949) and America (Scott, 1948) have shown in small animals that beryllium itself has direct toxic effect on the liver as well as the lung. It is premature to interpret these data. However, an attractive hypothesis—purely my own—supposes that beryllium is stored in the body, harmlessly if taken in slowly. Later, due to a change in medical status such as in pregnancy or an infection, the beryllium is mobilized and becomes pathogenic. Grier (Grier, Hood and Hoagland, 1949) and others have data to suggest beryllium displaces magnesium and the inhibition of enzymes follows with consequent widespread cellular changes, producing symptoms and signs. In leaving this subject, it is certainly fair to say that human experience and animal experimentation give strong evidence that certain beryllium compounds can produce profound changes in biological systems.

The diagnosis of beryllium poisoning rests on accurate demonstration of beryllium exposure. Spectrographic analysis will reveal beryllium in blood, urine and in biological tissue ante and post mortem in remarkably small quantities (Cholak and Hubbard, 1948). Tuberculosis must be carefully considered. Sarcoidosis, long held by some as the diagnosis in the industrially associated disease, is ruled out by the bad prognosis, severe respiratory disability, prevalence of gastro-intestinal symptoms and absence of X-ray changes in the bone. Finally, the pathologists with whom I have worked—Dr. David Freiman at the Massachusetts General Hospital especially—consider that beryllium poisoning has a

distinctive pathological picture. Fig. 2 shows a section made from the lung of a fatal case of acute beryllium pneumonia; next a similar example of the changes in the lung of a victim of chronic beryllium poisoning (Fig. 3); and, finally, an example of a case of that confusing entity, sarcoidosis (Fig. 4).

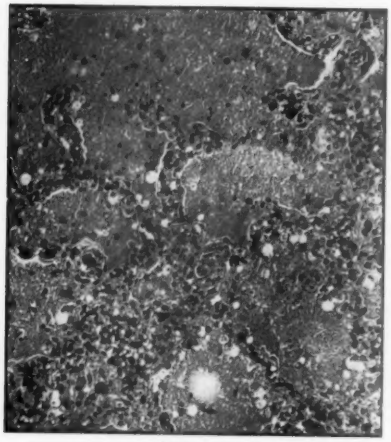

FIG. 2.

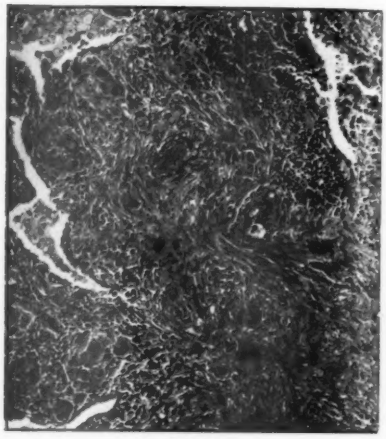

FIG. 3.

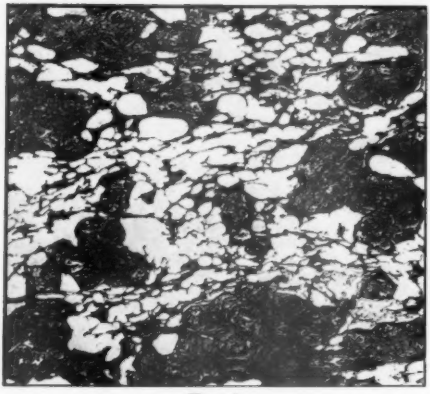

FIG. 4.

Histological sections of lung: FIG. 2.—Acute beryllium poisoning. FIG. 3.—Chronic beryllium poisoning. FIG. 4.—Sarcoidosis.

TREATMENT

The treatment of the cases of beryllium poisoning may briefly be mentioned. Acute beryllium pneumonitis has been attended by a low mortality ever since the seriousness of the process was recognized. In cases of chronic beryllium poisoning, antibiotics, chemotherapy, B.A.L., cytochrome C, sodium citrate, have been tried, all without success. Complete rest, support of morale, and judicious use of oxygen intermittently under pressure, have made these patients more comfortable but have not altered the prognosis. Temporary reversal or at least lessening of the X-ray densities in the lung of a few cases has followed the use of ACTH or cortisone as investigative agents and this makes us wonder if ACTH may not actually dissipate for a while the cellular infiltration which prevents oxygen from reaching the tissues in this disease.

Beryllium poisoning in the United States has become an important public health problem, because of the many industries using beryllium compounds (Williams, 1948).

TABLE I.—NUMBER OF KNOWN CASES OF BERYLLIUM POISONING

Process	Clinical designation Acute	Chronic
Extraction of Be from ore	300+	11
Machining Be	10	4
Fluor. powder mfg.	7	3
Fluor. lamp mfg.	5+	110+
Fluor. sign tubing mfg.	—	15
Be alloy mfg.	—	10+
"Neighbourhood cases"	—	9
Fluor. lamp salvage	—	4
Research work	—	6+
Radio tube mfg.	—	6
Ceramics	—	3
Silica crystal mfg.	—	2
Mining and handling beryl ore	—	—

From 1938 on, the rapid expansion of the fluorescent lamp industry accounts for most of our experience with the chronic disease. One plant using a phosphor containing about 12% beryllium reported all the cases of chronic beryllium poisoning between 1942 and 1947, but more recently other plants using a phosphor of between 2 to 3% beryllium have reported a few cases, occurring as long as six or more years after beryllium exposure ceased. A few individuals living very close to plants processing beryl ore or manufacturing fluorescent lamps have been victims of chronic beryllium poisoning. When the facts are known concerning the amount of certain beryllium compounds loosed in the near-by air and the proximity of these patients to the operations, the appearance of these so-called neighbourhood cases ceases to be mysterious. The 6 cases noted as due to research work took place after intermittent exposure to various levels of several beryllium compounds.

It is difficult to know how accurate the figures are, especially in the series where small numbers of cases of beryllium poisoning are reported. Ignorance of the toxicity of certain beryllium compounds, failure to elicit a history of beryllium exposure by physicians not aware of industrial uses of beryllium compounds and lack in the United States of central reporting of industrial disease make these figures unreliable but definitely not exaggerated.

Since beryllium oxide is encountered in every experience of worker illness, it may be considered the ætiologic common denominator. Depending on the source and processing, the compound beryllium oxide has varying physical characteristics. This may account in part for the irregular, unpredictable sickness experience encountered in industries using beryllium compounds. The study of these physical characteristics under the electron microscope was suggested in 1947 by C. R. Williams and carried out in 1948 by Kalmus and Tenney at the Los Alamos Scientific Laboratory.

Patterns of beryllium oxide samples from United States extraction plants vary in particle sizes in one preparation from an average of 0·3 micron to another of between one and two microns. One pattern showed so-called snowball aggregates and another a pattern called fish-hook under electron microscope study at a 9,000 times magnification.

I think it is easy to suppose that these two compounds might behave quite differently in gaining access to the body, in attacking cell membranes, or inciting phagocytosis once in the blood stream.

In contrast to beryllium oxide, beryllium phosphate has never been reported as producing disease. The electron microscope shows gigantic particles which would not easily enter the body.

My present view is that beryllium poisoning is a systemic disease rather than an exclusively pulmonary response to toxic insult. Apparently beryllium has a direct toxic effect on certain basic enzyme systems. Pathological study shows that beryllium intoxication causes a diffuse cellular infiltration of many tissues, which usually goes on to partial granulomatous formation and later irreversible fibrous replacement of functioning tissue with resultant clinical illness, great disability in most cases and frequent death.

The vast amount of material I have been able to study and use has been graciously made available to me by many colleagues—physicists and engineers as well as physicians. I want to mention the help and encouragement I have had from the late Dr. Leroy Gardner, Dr. J. C. Aub, Mr. Manfred Bowditch, Dr. Willard Machle, Professor Philip Drinker, Dr. H. M. Van Ordstrand, and the many clinicians who have allowed me to study their patients.

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Vanadium Pentoxide Poisoning

By H. WYERS, M.A., M.D., D.I.H.

VANADIUM was used by prehistoric primitive marine organisms and to-day is found in the blood of sea squirts and sea cucumbers. When these primitive organisms died, vanadium was deposited in oil-bearing strata. An important commercial source of vanadium is the soot of oil-burning liners and residues from oil refineries, from which it is extracted by fusing and filtration. During extraction, some vanadium is absorbed into the silica linings of the furnaces. Waste slag, including silica residue, is re-worked to extract vanadium.

Workers exposed to vanadium are pallid, show greenish-black discoloration of the central papillæ of the tongue and they suffer from palpitation and paroxysmal cough. Bronchitis is frequent and pneumonia is not uncommon. Radiological reticulation has been seen in 3 cases (Wyers, 1946).

Sjöberg (1949) has reported similar effects.

Vanadium salts are soluble and for this reason they are acute pulmonary irritants which act mainly on the upper respiratory tract. This is in agreement with clinical findings and with animal experiments reported by Sjöberg (1949) and by Lloyd Davies (1949). The latter showed that the intratracheal injection of vanadium metal, vanadium pentoxide and vanadium metavanadate in rats resulted in pulmonary œdema and acute bronchitis. After a few days the histological appearance reverted to normal; no evidence of chronic or interstitial inflammation was discovered.

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